FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF GABAPENTIN

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SUBMITTED BY

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KOMARAPALAYAM - 638 183

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Certificates

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF GABAPENTIN"** submitted by the student bearing **Reg. No. 26103014** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled "**FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF GABAPENTIN",** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment to the requirement for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by **Ms. SWETHA. KOORAPATI, [Reg.No:26103014],** during the academic year 2011-2012, under the guidance and supervision of **Dr. R. SAMBATH KUMAR** , Professor and Head Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam.

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CERTIFICATE

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DECLARATION

The work presented in this dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF GABAPENTIN",** was carried out by me, under the direct supervision of **Dr. R. SAMBATH KUMAR, M.Pharm., Ph.D.,** J.K.K. Nattraja College of Pharmacy, Komarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university and the thesis is ready for evaluation.

PLACE: **SWETHA KOORAPATI,**

DATE: **Reg. No: 26103014.**

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SWETHA . KOORAPATI,
(26103014).

Dedicated to

Almighty

My Beloved Parents

Contents

CONTENTS

LIST OF ABBREVIATIONS USED

API	: Active Pharmaceutical Ingredient
BLT	: Buoyancy lag time
C	: Centigrates
CDDS	: Controlled drug delivery system
CRDDS	: Controlled release drug delivery system
CMC	: Carboxy methyl cellulose
CO_2	: Carbon dioxide
HCL	: Hydrochloric acid
FDDS	: Floating drug delivery system
FT-IR	: Fourier transform infra red
FLT	: Floating lag time
5-FU	: 5-Fluro uracil
GFDDS	: Gatric floating drug delivery system
GI	: Gastro intestinal
GIT	: Gastro intestinal tract
GRDDS	: Gastroretentive drug delivery system
GRDFS	: Gastroretentive dosage forms
GRT	: Gastric retention time
HEC	: Hydroxy ethyl cellulose

HPC	: Hydroxyl propyl cellulose
HPLC	: High performace liquid chromatography
HPMC	: Hydroxy propyl methyl cellulose
IP	: Indian pharmacopeiae
KBr	: Potassium bromide
MCC	: Micro crystalline cellulose
MMC	: Migrating myloelectric cycle
MTC	: Maximum therapeutic concentration
NaHCO3	: Sodium bicarbonate
NaCMC	: Sodium carboxy methyl cellulose
PEO	: Polyethylene oxide
PGP	: P-glycoprotein
PVP	: Polyvinylpyrrolidone
SA	: Sustained action
SR	: Sustained release
TNF	: Tumour necrosis factor
USP	: United States Pharmacopeiae
UV	: Ultra violet

Chapter I

Introduction

INTRODUCTION

The commonly used and most convenient method of drug delivery is oral route of drug administration . Despite tremendous advancements in drug delivery the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration leading to high levels of patient compliance. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies, a brief gastrointestinal transit time, poor bioavailability and the existence of an absorption window in the upper small intestine for several drugs [1].

These difficulties have prompted researchers to design a drug delivery system which can remain in the stomach for prolonged and predictable period. Attempts are being made to develop a controlled drug delivery system, which can provide drug release at a pre determined, predictable and controlled rate. The denovo design of an oral CDDS should be primarily aimed at achieving more predictable and increased bioavailability of drugs[2]. For the successful performance of oral CRDDS the drug should have good absorption throughout the GIT, preferably by passive diffusion.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in GIT is to control the Gastric residence time (GRT) using gastro retentive dosage forms (GRDFS) that offer a new and better option for drug therapy.

1.1. Gastroretentive drug delivery system

Dosage forms which retained in the stomach for an extended period of time are called Gastro retentive dosage forms. These systems allow both time control and spatial drug liberation. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged

period of time before it reaches to its absorption site thus ensuring its optimal bioavailability, prolonged gastric retention improves bioavailability, reduces drug waste and improves the solubility of drugs that are less soluble in acidic pH environment.

Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. GRDFS can be used as carriers for drugs with so called absorption windows. These substances for example antiviral, antifungal and antibiotic agents (Cephalosporin's, Quinolones, Penicillin's, Sulphonamides, Amino glycosides, Tetracycline's etc) are taken up only from very specific sites of GIT. GRDFS can also have application in the for local drug delivery to the stomach and small intestine.

The controlled Gastric retention of solid dosage forms may achieved by the mechanism of Mucoadhesion, Floatation, Sedimentation, Expansion, Modified shaped systems or by the simultaneous administration of Pharmacological agents that delay the gastric emptying.

1.1.1 Potential drug used for Gastroretentive drug delivery systems

- Drugs those are locally active in the stomach.
  E.g. Misroprostol, Antacids etc.
- Drugs that have narrow absorption window in gastrointestinal tract (GIT).
  E.g. L-DOPA, Para aminobenzoic acid, Furosemide, Riboflavin etc.
- Drugs those are unstable in the intestinal or colonic environment.
  E.g. Captopril, Ranitidine HCl, Metronidazole etc.
- Drugs that disturb normal colonic microbes.
  E.g. Antibiotics against Helicobacter pylori. Etc.
- Drugs that exhibit low solubility at high P^H values.
  E.g. Diazepam, Chlordiazepoxide etc.

1.1.2 Drugs those are unsuitable for Gastro-retentive drug delivery system

- Drugs intended for selective release in the colon.
  E.g. 5-aminosalicylic acid and Corticosteroids etc.

- Drugs that have very limited acid solubility.
  E.g. Phenytoin etc.

- Drugs that suffer instability in the gastric environment.
  E.g. Erythromycin etc [3].

1.1.3 Drugs that would benefit from Gastro-retentive drug delivery

- CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine).
- Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics.
- Anti-hypertension drugs.
- Anti-diabetic agents for Type 2 diabetes.
- Drugs for local treatment of GI infections and gastric enzyme replacement [4].

1.1.4 Advantages of Gastroretentive drug delivery systems

- Enhanced bioavailability
- Better drug utilization.
- Improved efficiency in the treatment.
- Improved patient compliance.
- Site specific drug delivery.
- Sustained drug delivery / reduced frequency dosing.
- Reduced fluctuations of drug concentration.
- Absorption enhancement.
- Minimized adverse effects at the colon.

1.1.5 Limitations

- The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float.
- Drugs having irritant effect on gastric mucosa is not suitable candidates.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable E.g. Nifedipine [5].

1.2 Basic Gastrointestinal tract physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.14 this is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases [7].

1. **Phase I** (basal phase) lasts from 40 to 60 minutes with rare contractions.

2. **Phase II** (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. **Phase III** (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. **Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate[6].

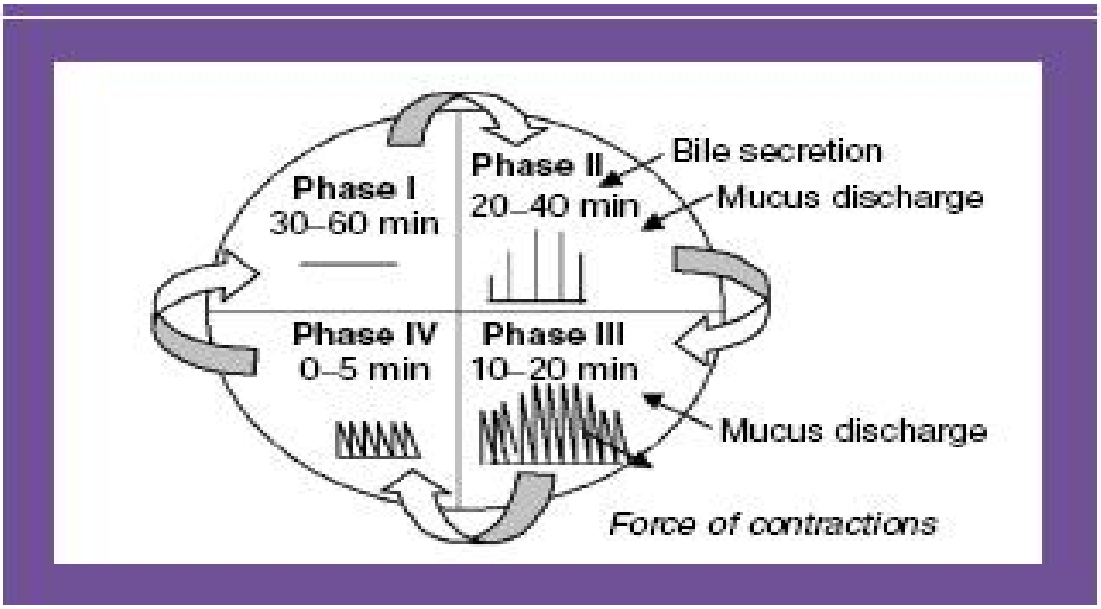


Figure 1: Gastrointestinal motility pattern.

Different features of the stomach:

- **Gastric PH** : Fasted healthy subject 1.1±0.15
  Fed healthy subject 3.6±0.4
- **Volume** : Resting volume is about 25-50 ml
- **Gastric secretion**: Acid, Pepsin, Gastrin, Mucus, and Some enzymes about 60ml with approximately 4 mol of hydrogen ions per hour.

Table1: Salient features of upper gastrointestinal tract

Parameter	Stomach	Small Intestine
pH range	1-4	5-7.5
Length (cms)	20	285
Diameter (cms)	15	2.5
Blood flow (L/min)	0.15	1.0
Microbial	<103	103-1010
Transit time (hours)	Variable	3±1
Absorbing Surface area (sq.mm)	0.1-0.2	120-200
Absorptive mechanisms	Passive diffusion, convective transport	All absorption mechanisms

1.3 Concept of Absorption Window

A major constraint in oral CRRDS is that not all the drugs are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of GIT only or absorbed to a different extent in various segments of gastrointestinal tract. Such drugs are said to have absorption window. Thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption after crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability [8].

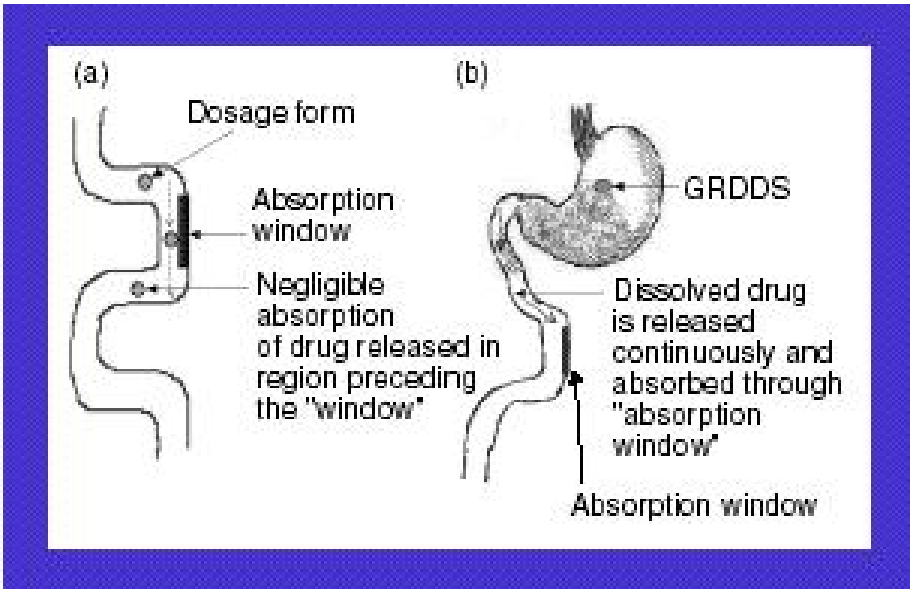


Figure 2: (a) Conventional drug delivery system, (b) GRDDS.

This absorption window is observed due to following factors

1) Physico chemical factors

a) pH- dependant solubility

b) pH-dependant stability

c) Enzymatic degradation

2) Physiological factors

a) Mechanism of absorption

b) Microbial degradation

3) Biochemical factors

a) Intestinal metabolic enzymes, cytochrome P450 (CYP3A)

b) Multi drug efflux pump, P-glycoprotein (PGP) present in the villus Tip of enterocytes in the GIT [9].

1.4 Factors Affecting the Gastro retentive System:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive

systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.

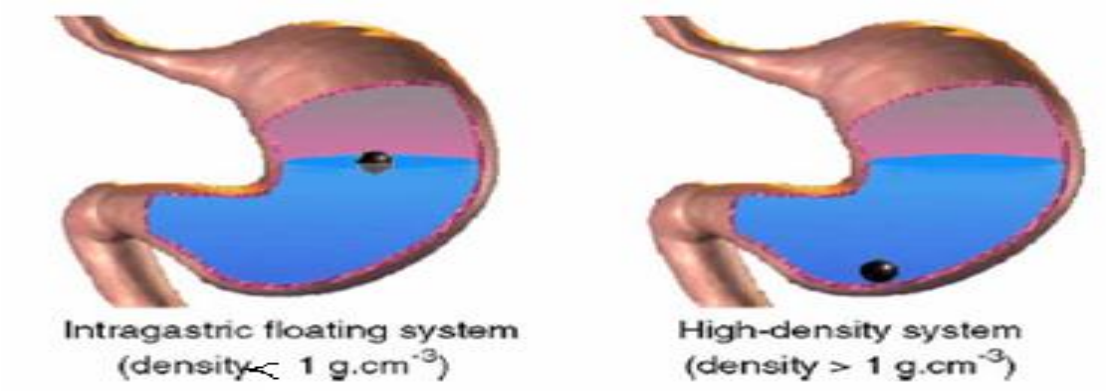


Figure 3: Schematic Representation of an intragastric floating system and a high density system in the stomach

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm[10].
- **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer[11].
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by 4 to10 hours with a meal that is high in proteins and fats
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.
- **Biological factors** – Diabetes and Crohn's disease, etc. also influences gastric retention[12.]

Table2: List of drugs formulated as single and multiple unit forms of floating drug delivery systems[13]

Dosage forms	Drugs
Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide di nitrate, Isosorbid mononitrate, p -Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline,Verapamil
Capsules	Pepstatin Verapamil HCl, Chlordiazepoxide HCl, Diazepam , Furosemide, L-Dopa, benserazide, Misoprostol Propranolol HCl , Ursodeoxycholic acid , Nicardipine
Granules	Prednisolone Cinnarizin , Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone Isosorbide mononitrate , Isosorbide dinitrate
Microsphere	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Powders	Riboflavin-59-phosphate Sotalol,Theophylline
Films	p-Aminobenzoicacid, Cinnarizine, Piretanide, Prednisolone, Quinidine gluconate

Table: 3 Marketed preparations of Gastro retentive technologies available in the International market

Brand Name	Active Ingredient	Remarks
Glumetza	Metformin	Polymer based
Cifran OD	Ciprofloxacin	Gas generating floating form
Pro QuinXR	Ciprofloxicin	Polymer based
Gabapentin GR	Gabapentin	Polymer based expandable film filled in capsule.
Baclofen GRS	Baclofen	Coated multilayer floating &swelling system
CoregCR (carvedilol)	Carvedilol	Gastro retention with Osmotic system
Madopar	L-DOPA-and Bensarazide	Floating Controlled Release capsules
Valrelease	Diazepam	Floating capsule
Topalkan	Aluminu-magnesium antacid	Floating Liquid alginate preparation.
Almagate FlatCoat	Aluminu-magnesium antacid	Floating Dosage form
Liquid Gavison	Aluminium hydroxide	Effervescent floating Liquid alginate preparation.
Cytotec	Misoprostal	Biilayer floating capsule

1.5 Different Techniques of Gastric Retention

Various techniques have been made to retain the dosage form in the stomach as a way of increasing the retention time. These techniques include, floating dosage forms[14], swelling and expanding system, mucoadhesive systems , high density system modified shape systems Gastric emptying delaying devices and co-administration of gastric delaying drugs[15,16]. Among these, the floating dosage forms have been used most commonly.

I). High-density systems

II). Floating systems

III). Superporous hydrogels

IV). Swellable systems

V). Bioadhesive or mucoadhesive systems

VI). Magnetic systems[17]

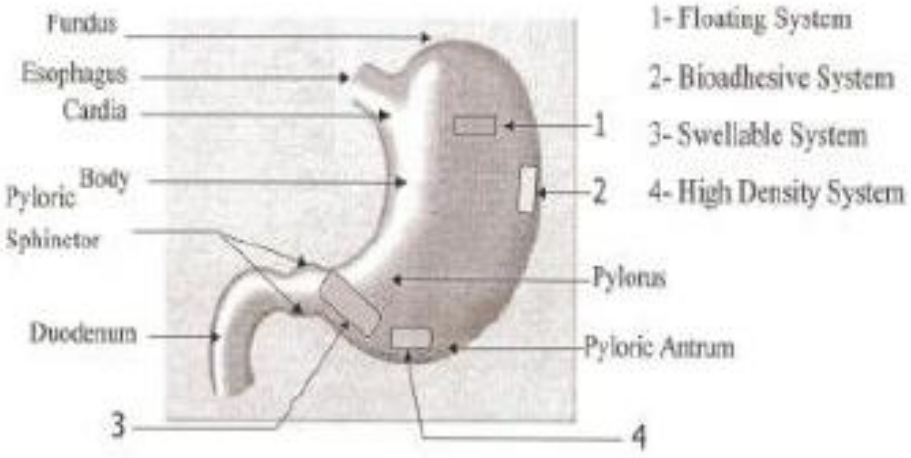


Figure 4: Different Gastroretentive systems in the Gastrointestinal tract.

I) High-density systems

These formulations have a density of 2.4-2.8 g/cm^3 greater than the stomach contents. (1.004 g /cm^3). When the patient is upright small high-density pellets sink

to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time[18].

Drawback: these are technically difficult to manufacture, with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8 g/cm$^{3.}$ Barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

II) Floating Drug Delivery System

The concept of FDDS was described in the literature as early as 1962. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine[19] .FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

Formulation of this device must comply with the following criteria

1) It must have sufficient structure to form a cohesive GIT barrier.

2) It must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010).

3) It should dissolve slowly enough to serve as a drug reservoir[20].

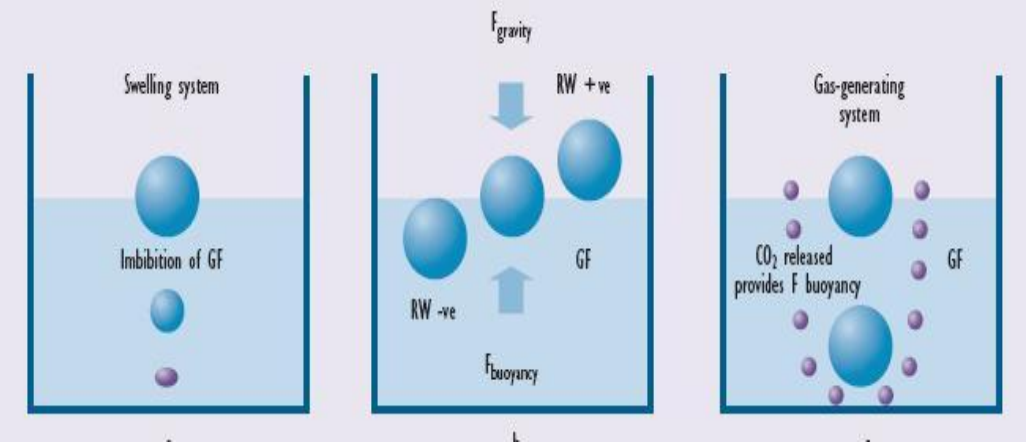


Figure 5: Mechanism of floating system

Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy two distinctly different technologies have been

Utilized in the development of FDDS.

1) Effervescent FDDS

2) Non- Effervescent FDDS

1) Effervescent floating dosage forms

A. Gas generating Systems

These are the matrix types of systems which are prepared by using swellable polymers like methylcellulose, HPMC and Chitosan based polymers as well as various effervescent compounds like sodium carbonate, calcium carbonate, tartaric acid and citric acid[21] .They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 liberated and gets entrapped in the swollen hydrocolloids, which provides buoyancy to the dosage forms.

i) Single unit systems (Tablets and capsules)

1 In these systems effervescent substances are incorporated in the hydrophilic polymer, and co_2bubbles are trapped in the swollen matrix[22] .

2 Bilayer or multilayer systems have also been designed. in these systems drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers.

3 Further refinements involve coating the matrix with a polymer which is permeable to water, but not to co_2[23].

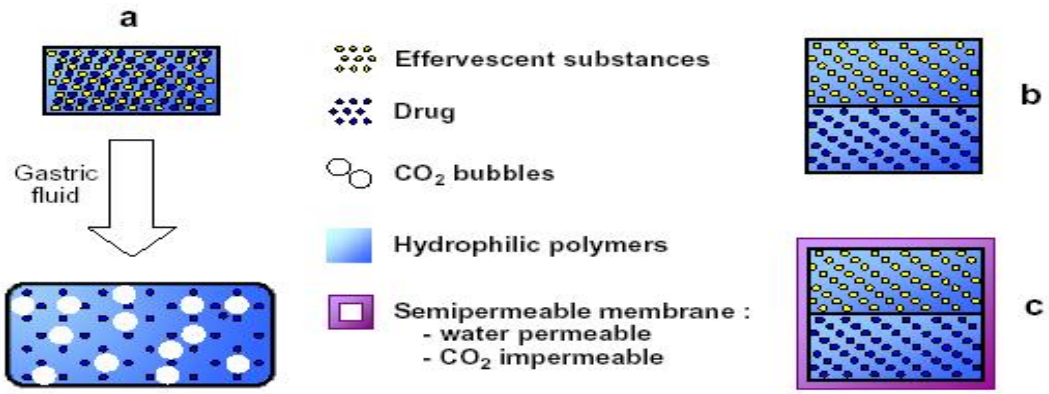


Figure 6: Monolayer drug delivery system (a) Bi layer gas generating system, with(c) or without (b) semipermiable membrane.

ii) Multiple unit type Floating Pills

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system[24].

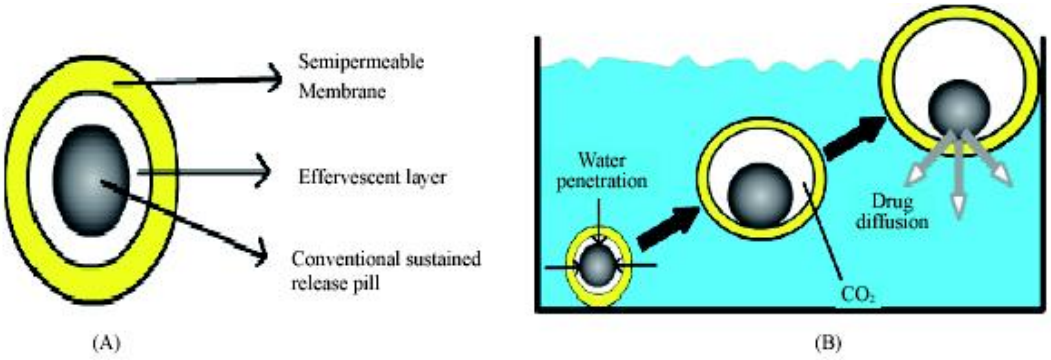


Figure7: Schematic Representation of floating a pill. (A) Different layers. (B). Mechanism of floatation via gastric retention.

iii) Floating System with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO_2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO_2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads [25].

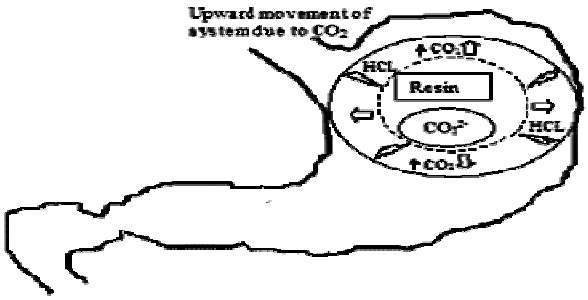


Figure 8: Pictorial Presentation of working Effervescent floating drug delivery system based on Ion exchange resin.

iv) Raft-Forming Systems

In these systems, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as Aluminium hydroxide or calcium carbonate to

reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for Gastro esophageal reflux treatment as with liquid Gaviscon [26].

Figure 9: Schematic illustration of the barrier formed by a raft-forming system

v) Low Density Systems:

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragits, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used [27].

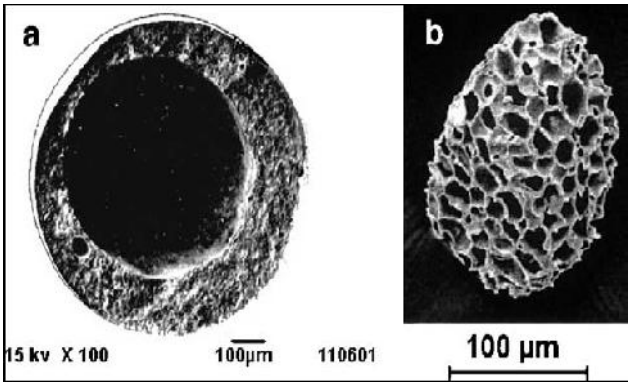


Figure 10: a) Microballoons (b) Foam-particles

B. Volatile liquid / Vacuum containing systems

These include the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature [10].

i) Intra-gastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

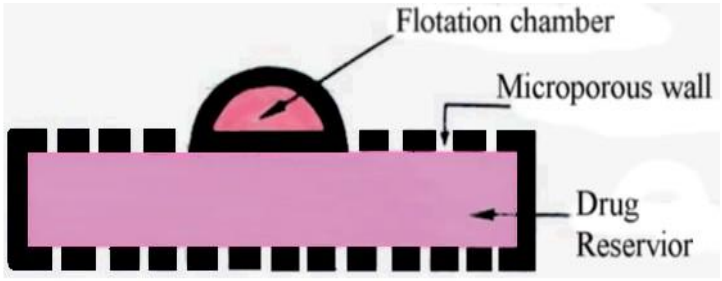


Figure 11: Intra gastric floating Gastrointestinal Drug Delivery Device

ii) Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatine capsule[28].

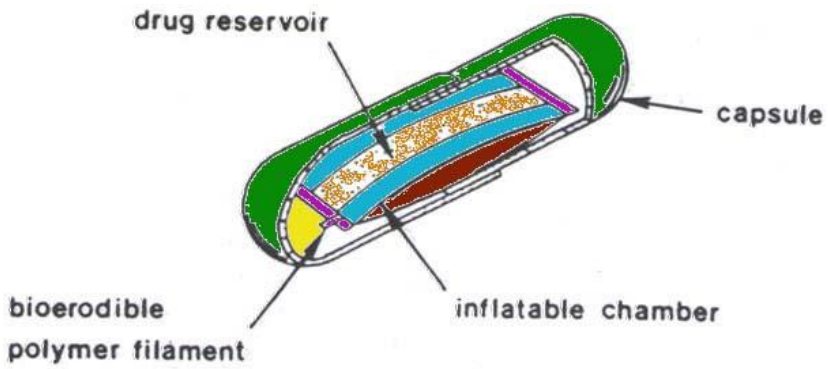


Figure 12: Inflatable gastrointestinal delivery system

iii) Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio-erodible capsule. In the stomach the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable supports inside forms a deformable hollow polymeric bag that contains a liquid that gasify at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment [29].

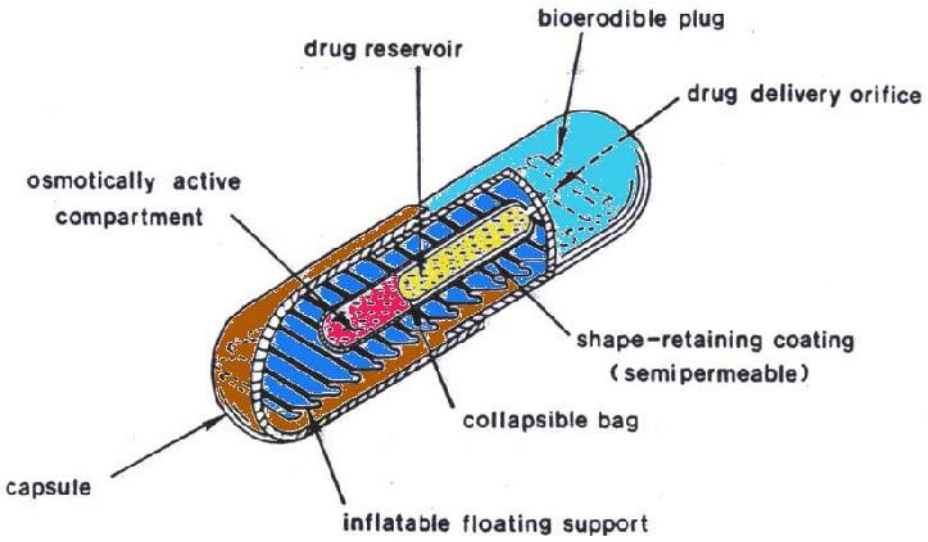


Figure13: Intragastric Osmotically Controlled Drug DeliverySystem

2) Non-Effervescent FDDS

Non-effervescent floating drug delivery systems use a gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers. The formulation method includes the intimate mixing of drug with a gel forming hydrocolloid. After oral administration this dosage form swell in contact with gastric fluids and attains a bulk density <1. The air entrapped with in the swollen matrix imports buoyancy to these dosage forms. The swollen gel like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass..

Excipients used most commonly in these systems include Hydroxypropyl methylcellulose (HPMC), Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Sodium alginate, Calcium chloride, Polyethylene oxide and Polycarbonates[30].

A. Hydro Dynamically Balanced system;

These are single-unit dosage form, containing one or more gel-forming Hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC), Hydroxy ethyl cellulose (HEC), Hydroxyl propyl cellulose (HPC), Sodium carboxy methyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans and alginic acid are also used. The polymer is mixed with drugs and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymer produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy [31].

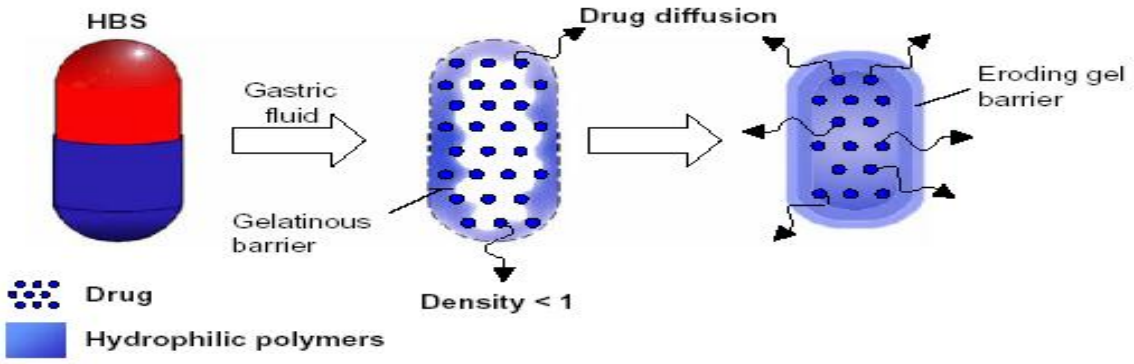


Figure14: Working principle of Hydro Dynamically Balanced system

1. Single Layer Floating Tablets are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.

2. A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

B. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours [32].

III) Super porous hydrogel system

These swellable systems differ sufficiently from the conventional types to warrant separate classification. These are used to improve gastric retention time (GRT) super porous hydrogels have a average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting

through numerous interconnected open pores (klusner2003). They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material[33].

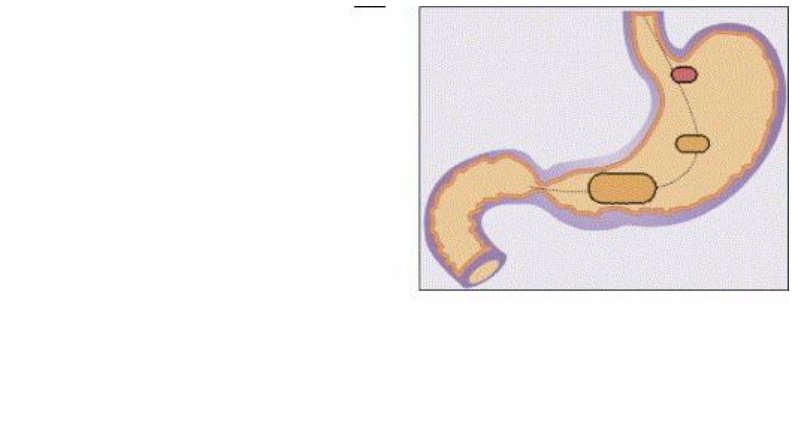


Figure 15: Schematic Representation Super porus hydrogel

IV) Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. The configurations required to develop an expandable system to prolong gastric retention time (GRT) are

1) A small configuration for oral intake,

2) An expanded gastro retentive form, and

3) A final small form enabling evacuation following drug release from the device.

Unfoldable systems are made of biodegradable polymers and are available in different geometric forms like tetrahedron, ring or planner membrane of bioerodible polymer compressed within a capsule which extends in the stomach[11].

Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water.

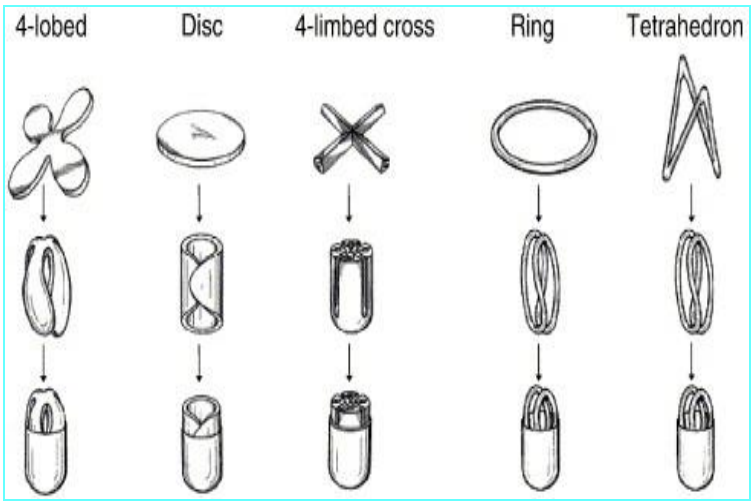


Figure 16: Different geometric forms of unfoldable systems

Drawbacks: Storage of much easily hydrolysable, biodegradable polymers relatively short-lived, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy .

V) Bio/Muco-Adhesive Systems

These are used to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion is, the dosage form can stick to the mucosal surface by different mechanism. Materials used for bioadhesion are poly acrylic acid, chitosan,

cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc.

Draw back: Rapid turnover of mucous in the gastrointestinal tract (GIT).

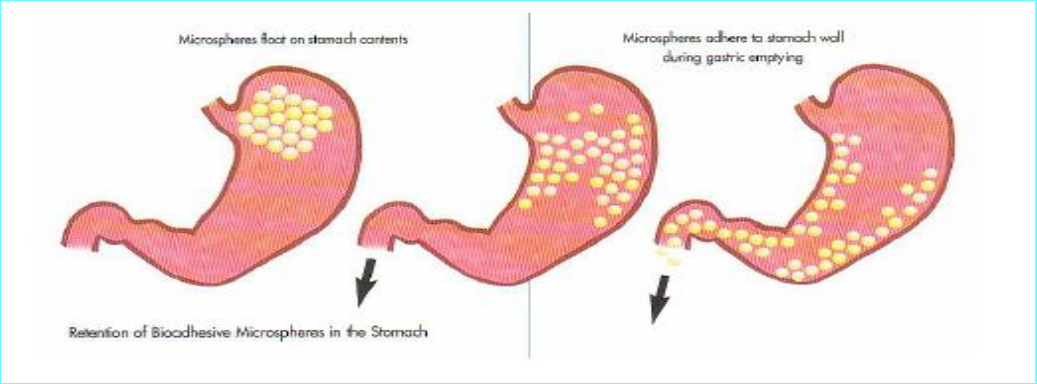


Figure17: Schematic Representation of Bioadhesive microspheres

VI) Magnetic Systems:

This approach is used to enhance the gastric retention time (GRT), and is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance[34].

DISEASE PROFILE

INTRODUCTION :

Epilepsy was one of the first brain disorders to be described. It was mentioned in ancient Babylon more than 3,000 years ago. The strange behavior caused by some seizures has contributed through the ages to many superstitions and

prejudices. The word epilepsy is derived from the Greek word for "attack." However, in 400 B.C., the early physician Hippocrates suggested that epilepsy was a disorder of the brain -- and we now know that he was right[35].

More than 2 million people in the United States -- about 1 in 100 have experienced an unprovoked seizure or been diagnosed with epilepsy. For about 80 percent of those diagnosed with epilepsy, seizures can be controlled with modern medicines and surgical techniques[36]. However, about 25 to 30 percent of people with epilepsy will continue to experience seizures even with the best available treatment.

Epilepsy :

Epilepsy is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions, and behavior, or sometimes convulsions, muscle spasms, and loss of consciousness[37]. During a seizure, neurons may fire as many as 500 times a second, much faster than normal. In some people, this happens only occasionally; for others, it may happen up to hundreds of times a day.

The risk of premature death in people with epilepsy is 2-3 times higher than the general population. The exact cause of the increased risk is not known in most cases i.e. the cause of sudden unexpected death in some patients[38]. However, some deaths are related to the circumstances around a seizure such as a serious accident during a seizure.

CLASSIFICATION OF EPILEPTIC SEIZURES

Epilepsy can broadly be divided into two categories: idiopathic where there is no known cause, and secondary seizures where there is known cause. Seizures can be either generalized or partial (or focal). In generalized seizures, both halves of the brain are simultaneously affected. In partial seizures, the abnormal

electrical discharge starts from a focus in one side of the brain. Later, this may spread to the other side. This spread is called secondary generalization.

Generalized Seizures

In generalized seizures, patients suddenly stop what they are doing, the eyes and head turn to one side and the body becomes stiff. This is usually followed by several jerks of the hands and legs, groaning and frothing from the mouth[39].Generalized seizures consist of many different seizure types, of which the primary generalized tonic-clonic seizure (GTCS) is the most common.

Tonic-clonic seizure

In a generalized tonic -clonic seizure the patient loses consciousness, falls down, sometimes with a scream, and develops a generalized stiffness[40]. Breathing stops, as all the muscles of the trunk are in spasm, the head is retracted, the arms flexed and the legs extended. After a while, this tonic phase is followed by the clonic phase, when the muscles alternately contract and relax, resulting in clonic movements.Either the tonic phase or the clonic phase can predominate in the seizureGeneralized tonic -clonic seizures can also occur due to secondary generalization in partial epilepsies[7].

Clonic seizures

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs). When the frequency of jerks diminishes the amplitude of the jerks does not diminish.

Tonic seizures

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is deviation of eyes and head towards one side, sometimes rotation of the whole body.

Absence seizures

These are short periods of loss of consciousness lasting only a few seconds (not more than half a minute). They are of sudden onset, there are usually no, or only minimal motor manifestations. There is a blank stare, brief upward rotation of the eyes and an interruption of ongoing activity. The child is unresponsive when spoken to. It is suddenly over, and the child continues what he was doing before the seizure. People are unaware that these absences are epileptic seizures[41]. Absences are easily provoked by hyperventilation.

Myoclonic seizures

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb, or more widespread and bilateral. They may be single jerks, or jerks repeated over longer periods. They are often seen in combination with other seizure types occurring in special epileptic syndromes.

Infantile spasms

Patients have flexor spasms of the head, bending of the knees and flexion with abduction of the arms. They occur in the first year of life, and are very difficult to treat.

Partial Seizures

Partial seizures are divided into two groups, simple partial seizures where consciousness is maintained and complex partial seizures where there is an impairment of consciousness.

Simple partial seizures

In simple partial seizures, some patients may experience either motor or sensory phenomena. Such seizures arise from a specific area of the brain, with the patient being fully or partly aware of the event. In motor seizures, the focus is in the primary motor cortex. The psychic symptoms may consist of changes in mood, memory, or thought . May be distorted perceptions or problems with language.

Structured hallucinations could occur. These simple partial seizures are usually only recognized as epileptic seizures when they develop into generalized seizures[42].

Complex partial seizures

Here the patient has impaired consciousness, but not complete loss of consciousness. He is slightly aware of what is going on, but he cannot respond to anything, neither can he change his behaviour during an attack. The seizure usually starts with an aura which can be of many types such as, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste or with changes in perception.After the attack, there is complete amnesia regarding the attack.[43]

SYMPTOMS

Symptoms vary from person to person. Some people may have simple staring spells, while others have violent shaking and loss of alertness. The type of seizure depends on the part of the brain affected and cause of epilepsy[44].

Most of the time, the seizure is similar to the previous one. Some people with epilepsy have a strange sensation (such as tingling, smelling an odor that isn't actually there, or emotional changes) before each seizure.[45]

DIAGNOSIS OF EPILEPSY

It is essential that patients with episodes such as described above be accompanied by a witness who can describe the episodes in detail. More often than not, epilepsy can be diagnosed on the basis of reports of patients and eyewitnesses. No laboratory test can replace a clear description provided by the eyewitness.[46] Those who develop epilepsy for the first time require investigations to identify the underlying cause. These investigations include EEG, and imaging tests such as CT scan or MRI of the brain.

Treatment

Treatment for epilepsy may involve surgery or medication.If epilepsy seizures are due to a tumor, abnormal blood vessels, or bleeding in the brain, surgery to treat these disorders may make the seizures stop[47].

Medication to prevent seizures, called anticonvulsants, may reduce the number of future seizures.

- Your dosage may need to be changed from time to time. You may need regular blood tests to check for side effects.
- Always take your medication on time and as directed. Missing a dose can cause you to have a seizure. Never not stop taking or change medications without talking to your doctor first.
- Many epilepsy medications cause birth defects[48]. Women wishing to become pregnant should tell the doctor in advance in order to adjust medications.

Epilepsy that does not get better after two or three anti-seizure drugs have been tried is called "medically refractory epilepsy."

- Surgery to remove the abnormal brain cells causing the seizures may be helpful for some patients.
- Surgery to place a vagus nerve stimulator (VNS) may be recommended. This device is similiar to a heart pacemaker. It can help reduce the number of seizures.

Prevention

Generally, there is no known way to prevent epilepsy. However, proper diet and sleep, and staying away from illegal drugs and alcohol, may decrease the likelihood of triggering seizures in people with epilepsy.Reduce the risk of head injury by wearing helmets during risky activities; this can help lessen the chance of developing epilepsy[49].

Persons with uncontrolled seizures should not drive. Each state has a different law that determines which people with a history of seizures are allowed to drive[50]. If you have uncontrolled seizures, you should also avoid activities where loss of awareness would cause great danger.

Chapter II

Literature Review

LITERATURE REVIEW

C. Sharon Kumar et al.,[51] prepared and characterized the floating microspheres of gabapentin by using the solvent evaporation method. The prepared floating gabapentin microspheres were evaluated for different evaluation parameters such as percentage yield, particle size determination, drug content determination, Encapsulation efficiency, *In-Vitro* buoyancy, *in-vitro* drug release. The *in vitro* drug release revealed that batch C was having 75% cumulative release at the end of 12 th hour when compared with batch A & B ,due to increase in polymer concentration as seen in formulation C (1:3). The release kinetics of Gabapentin followed Supercase II transport diffusion.

Ferdous et.al.,[52] developed floating tablets of theophylline using methocel K4M. Sodium bicarbonate and citric acid were incorporated as gas generating agents. It has been observed that in all cases increase of the amount of floating agent caused a decrease of the floating lag time. Increase of theophylline load showed an increase of the floating lag time, which was independent of floating agent content. The release mechanisms were explored and explained with kinetic models. Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was mainly dependent on presence of relative amount of theophylline, polymer and floating agent.

Shailesh T. Prajapatiet al., [53] developed the Floating matrix tablets of Domperidone using PEO WSR 303, HPMC and sodium bicarbonate by simplex lattice design. Tablets were evaluated for in vitro floating ability and drug release study. It was observed that as the PEO increased, release rate constant decreased. Mechanism of drug release was anomalous type and dependent upon proportion of HPMC and PEO. It was observed that independent factors had significant contribution on all dependent variables.

Md. Mofizur Rahman et al.,[54] evaluated the effect of hydrophilic polymers on the release profile of drug from matrix system. Matrix tablets of salbutamol sulphate were prepared by direct compression process using methocel K100M CR polymer. Release kinetics of salbutamol sulphate from these sustained release matrices in distilled water using USP paddle method with for 8 hours were studied. Higher polymer content (70%) in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity. At lower polymeric level (30%), the rate of drug release was elevated. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug.

Rakesh Patel, Ashok Baria[55]**,** prepared a sustained release matrix tablet of Theophylline and different grades of hydroxypropyl methyl cellulose were evaluated for gel forming properties.. The amounts of HPMC K-4M (X1) and HPMC K-100M (X2) were selected as independent variables. Cumulative % release of drug for 1st hour and 8th hour were selected as dependent variables.The results of the full factorial design indicated that a low amount of HPMC K-100M and a high amount of HPMC K-4M favors sustained release of Theophylline from matrix tablet. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. Finally, process optimization was carried out to optimize the process parameters like kneading time, mixing time, thickness of the tablet and lubrication time.

R. Gendle et al.,[56] developed sustained release tablets of highly water soluble Tramadol HCl using polymers (HPMC K100M, HPMC K15M, HPMC K 4M) as suitable hydrophilic matrix system. Sustained release tablet of Tramadol HCl (dose 50mg) were produced by wet granulation method. After the evaluation of physical characteristics of tablets. The dissolution test was performed in 0.1 N HCl for two hr. and phosphate buffer pH 6.8 for ten hr. The release profile remains unchanged after three months storage of tablets. The best fit release kinetics was achieved with

the zero order plot followed by the Higuchi and Korsmyer and Peppas equation. The data obtained proved that the formulations are useful for a sustained release of Tramadol HCl due to the percentage released after 12 hr. is nearly to 100%.

P.N.Kendre et al.,[57] developed single unit controlled delivery system of Theophylline and was formulated as floating matrix tablet by direct compression method using gas generating agent (sodium bicarbonate) and various viscosity grades of hydrophilic polymers (HPMC K15M, K4M; HPC and Carbapol 934P). The tablets swelled and eroded upon contact with release medium (0.1 N HCl) at 37 0C. The release rate could efficiently be modified by varying the matrix forming polymer, the use of polymer blends and the addition of water soluble or water insoluble fillers (such as dicalcium phosphate, lactose or mannitol). Fitting the in-vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Ravala et al.,[58] prepared Ranitidine hydrochloride floating matrix tablets based on low density powder. The tablets were prepared by the direct compression technique, using hydrophilic matrix polymers HPMC K4M, HPMC K15M, HPMC K100M, sodium alginate, psyllum,sesbania gum, guar gum, and gum acacia, with or without low density copolymer. . Incorporation of the highly porous low density copolymer in the matrix tablets provides densities that are lower than the density of the release medium. low density copolymer was sufficient to achieve proper *in vitro* floating behavior for at least 8 h. Unlike most conventional floating systems, these tablets floated almost immediately upon contact with the release medium.

Jaimini and Tanwar [59] prepared a gastro retentive drug delivery system of Famotidine employing two different grades of methocel K100 and methocel K15M by effervescent technique; these grades of methocel were evaluated for their gel forming properties. Sodium bicarbonate, citric acid were incorporated as a gas-generating agents. . Decrease in the citric acid level increased the floating lag time

but tablets floated for longer duration. The tablets with methocel K100 were found to float for longer duration as compared with formulations containing methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Sandra Strübing et al.,[60] developed floating kollidon® SR matrix tablets containing propranolol.Tablet floating started immediately and continued for 24 h. Floating strength was related to Kollidon® SR level with improved floating characteristics for samples with a high polymer/drug ratio. The influence of the polymer content on swelling characteristics was found to be only marginal. Furthermore, the new method of benchtop MRI was introduced to study the water diffusion and swelling behaviour non-invasively and continuously.

M.Harris Shoaib et al.,[61] developed a once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

Pare A et al.,[62] developed amlodipine besylate effervescent floating tablets in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid.. F10 formulation showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours and whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.

Patel Amit et al.,[63] prepared floating drug delivery system of famotidine. Six formulations were prepared containing gel-forming agent (HPMC K4M) and retardant (Na-CMC) in different ratio and it was found that gas generating agent (NaHCO3) reacts with HCl and liberates CO2 which creates pores in tablet and elevates swelling and maintains buoyancy. The prepared tablets were evaluated for content uniformity, hardness, friability, buoyancy, swelling index and *in-vitro* dissolution studies. Further selected formulation was subjected for short term stability studies for one and two month at temperature of 25°c and 40°c respectively

Shreeraj H. Shah et al.,[64] developed a gastric floating drug delivery system (GFDDS) containing Levofloxacin against the H.pylori infection.Stability study was also performed after storage at 40°C/75% RH for three months.The batch containing combination of HPMC K4M, HPMC K100M and Carbopol 974P (i.e. L12) showed total floating lag time more than 24 hrs. The batch L12 showed the highest swelling index among all the prepared batches (i.e. 95%). The batch L12 was chosen as the optimized batch since it was also stable for three months during stability study.

Senthilkumar et al., [65] prepared and evaluated floating microsphere using Rabeprazole sodium (RS) as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the solvent evaporation method using different polymers like HPMC and MC ,to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and there by improved bioavailability. HPMC Containing microspheres showed a desirable high drug content, flow property, buoyancy, adequate release characteristics hence, formulations prepared by such polymer are suitable for development of gastro retentive dosage forms.

Reddy Sunil et al.,[66] developed bilayered tablets containing Glimepride for immediate release using sodium starch glycolate as super disintegrant and Metformin hydrochloride (HCl) for sustained release by using Hydroxyl propyl

methyl cellulose (HPMC K 4M) and Sodium Carboxy Methyl cellulose (SCMC) as the matrix forming polymer, and PVPK-30 as binder... The polymer (HPMC K4M, SCMC) and binder PVPK-30 had significant effect on the release of Metformin HCl matrix tablets (F5). Thus formulated bilayer tablets provided immediate release of Glimepride and Metformin HCl as sustained release over a period of 8 hours. Stability studies and FT-IR studies clearly indicated that there is no drug –polymer interaction.

Baumgartner S et al.,[67] developed floating matrix tablets containing Hydroxypropyl Methyl Cellulose , which after oral administration are designed to prolong the gastric residence time , increase the bioavailability and diminish the side effects of irrititating drugs.The importance of the composition optimization , the formulation aspect and characterization of the tablets were examined.The investigation showed that the talet composition and mechanical strength have great influence on the floating and drug release properties of the tablets. They concluded that the drug release from the tablets followed non-Fickian transport.

Vishal G. Karkhile et al.,[68] prepared floating tablet of Furosemide by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG-6000 is used as complexing agent for increasing solubility of Furosemide in water. Hydroxypropylmethylcellulose, sodium bicarbonate and carbapole were used as Matrixing agent gas generating agent and floating enhancers respectively. Further, tablets were evaluated for in vitro release characteristic for 8 hrs. The data of *in-vitro* dissolution study shows that the zero order plots were found to be fairly linear as indicated by their high regression value (R2=0.9772 to 0.9911). To confirm the exact mechanism of drug release from different formulation, the data was fitted to Korsmeyer Peppas equation.

Chapter III

Aim and Objective of Work

AIM AND OBJECTIVE

- The majority of the drugs are absorbed in the upper part of the small intestine.
- Gabapentin is an anti epileptic drug and also used now-a-days to treat neuropathic pains. It is rapidly absorbed from GIT and plasma half life is about 5-7 hours. Its short biological half life and once daily administration of conventional tablet, which maintains study state of concentration was difficult, to overcome this problem the present work is proposed for the sustained release effervescent floating dosage form of Gabapentin.
- Conventional dosage forms reside in stomach and intestine for only short period. So there is a need of dosage form that increases residence time of drugs in absorption site.
- Gastroretentive dosage forms are used to increase residence time of drugs. Among the gastroretentive systems effervescent floating tablets have more advantages.
- The aim of the present work is to formulate gastroretentive dosage form of gabapentin by effervescent floating tablet technique by using various polymers.
- One of the purpose of this formulation was to maintain *in vitro* buoyancy as well as duration of floating stable for at least 12 hours and *invitro* dissolution study.
- To study the effect of polymer grade or viscosity: In the present investigation Hydroxypropyl Methylcellulose K100M, Sodium Carboxy Methyl Cellulose, Polyethylene Oxide, were used to increase duration of floating and release rate .
- Rate of drug release and mechanism of drug release from the designed tablets were evaluated.

Chapter IV

Plan of Work

PLAN OF WORK

To achieve the above objectives the experimental work was framed as below

Phase-I:

1. Pre-formulation study of pure drug gabapentin
2. Compatibility study
    i) Fourier transform infrared spectroscopy (FT-IR)

Phase-II:

1) Formulation of effervescent floating tablets of Gabapentin.
    A) Determination of effect of sodium bicarbonate on floating lag time
    B) Formulation of Gabapentin (600 mg) effervescent floating tablets with different concentrations of HPMC K100M, Sodium CMC , PEO.
2) Evaluation of precompression blend for various parameters like Angle of Repose, Bulk density, Tapped density and Carr's index.
3) Evaluation of effervescent floating tablets of Gabapentin
    A) To determine floating lag time and total buoyancy time.
    B) To evaluate prepared matrix tablets for various physical parameters like Weight variation, Thickness, Hardness and Friability.
    C) Determination of *in vitro* drug release from the formulations in 0.1N HCl for 12 hours.
    D) Determination of percentage swelling of all formulations.
    E) To determine content uniformity of effervescent floating tablets.
    F) *In vitro* release data was fitted into various kinetic models for suggesting the suitable mechanism of drug release.
4) Selection of the best batch of tablets based on the *in vitro* release kinetic data.
5) Determination of drug-excipients interaction of optimized formulations.
6) Accelerated stability study of the optimized formulation.

Chapter V

Theoritical Background

THEORITICAL BACKGROUND PROFILES

DRUG PROFILE

Drug information[69]

Generic name **:** Gabapentin

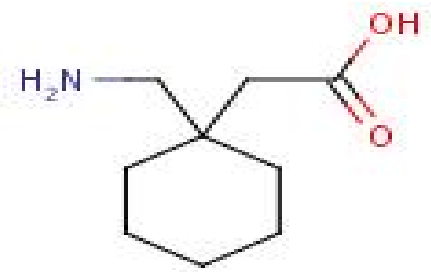
Trade name : Neurotin

Chemical name : 2-[1-(amionmethyl) cyclohexyl] acetic acid

Empirical formula : $C_9H_{17}NO_2$

Molecular weight : 171.24

Structure:



Physico chemical profile:

Description : White or partially white amorphous powder

Melting point : 162-166 C

Solubility : Freely soluble in water, acidic, alkaline solutions

Partition co-efficient : log p equal to 1.4

Pharmaceutical profile:

Dosage forms and dose

Tablets 100,300,400,600,800 mg Capsules –100,300,400mg

Pharmacopoeial status

Official in USP and IP

Analytical profile:

Chromatographically analyzed by HPLC at 210 nm.

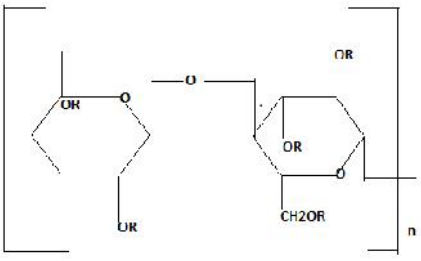
Pharmacokinetic profile:

Oral absorption	:	60% .Food has slight effect on the rate and absorption (14% increase in auc)
Plasma half life	:	5-7 hours
Volume of distribution	:	58±6 L
Protein binding	:	less then 3%
Metabolism	:	not apparently metabolized
Clearance	:	140 ml/min
Excretion	:	renal
Pharmacological profile	:	Antiepileptic

EXCIPIENT PROFILE

HYDROXYPROPYL METHYLCELLULOSE[70]

Non-proprietary names	:	Hydroxypropyl methylcellulose
Chemical name	:	Cellulose, 2-hydroxypropylmethylether
Molecular Weight	:	Approx. 86,000 g/mol
Types and grades	:	Various grades of HPMC, official in USP, BPC, IP, are frequently employed as polymer for controlled drug release. For BPC/IP grades the name is followed by a number indicating the apparent viscosity of a 2% w/v solution in mill Pascal seconds at 20°C. For USP grade HPMC, the name is followed by a four-digit numbers. The first two digits refer to the approximate content of the methoxy ($-OCH_3$) groups and the second digit refers to the approximate content of the hydroxypropoxy group ($-CH_2CHOCH_3$) in percent, calculated on dry basis (105^oc for two hours).



Structure of HPMC

Physiochemical properties

Apparent density	:	0.25-0.70 g/cm^3
Particle size	:	> 95% through 40 mesh
Percentage moisture	:	3% (maximum)
Specific gravity	:	Approximately 1.3
Surface activity	:	Provides some surfactancy in solutions. Surface tensions for such solution range from 42-56 dynes/cm
Gel formation	:	Undergoes a reversible transformation from sol to gel upon heating and cooling, respectively.
Glass transition	:	155^{o}C
Solubility	:	Soluble in cold water, forming a viscous colloidal solution, practically insoluble in hot water, acetone and toluene, insoluble in alcohol, ether and chloroform, but soluble in mixture of methyl alcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixture of methylene chloride and isopropyl alcohol and other organic solvents.
Stability	:	Very stable in dry conditions. Solutions are stable at pH 3.0-11.0. Aqueous solutions are liable to be affected by microorganisms.
Storage	:	To be stored in a tight container and in a cool place
Safety	:	Human and animal feeding studies have shown HPMC to be safe.

Table 4: Methocel grades, their viscosities and application

Grade	Viscosity	Application
E5	5	Film coating, Granulating agent
E15	15	Film coating, Granulating agent, Suspending agent
E50	50	Film coating, Granulating agent
E4M	4000	Sustained release, Medicated gel, Thickening agent
E4MCR	4000	Sustained release
E10M	10,000	Sustained release
E10MCR	10,000	Sustained release
F4M	4000	Eye drops, Suspending agent
K4M	4000	Sustained release, Suspending agent
K15M	15,000	Sustained release
K15MCR	15,000	Sustained release
K100M	100,000	Sustained release
K100MCR	100,000	Sustained release

SODIUM BICARBONATE[71]

Nonproprietary Names	:	BP: Sodium bicarbonate JP: Sodium bicarbonate PhEur: Natrii hydrogenocarbonas USP: Sodium bicarbonate
Synonyms	:	Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.
Description	:	Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.
Chemical Name	:	Carbonic acid monosodium salt
Empirical Formula	:	$NaHCO_3$
Molecular Weight	:	84.01 g/mol
Structural Formula	:	$NaHCO_3$
Melting point	:	270°C (with decomposition)
Functional Category	:	Alkalizing agent; therapeutic agent.
Applications	:	Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are

weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.

Stability : When heated to about 50°C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, sodium bicarbonate is completely converted into anhydrous sodium carbonate.

Storage Conditions : Stored in a well-closed container in a cool, dry place.

Table 5: Uses of Sodium bicarbonate

Use	Concentration (%)
Buffer in tablets	10–40
Effervescent tablets	25–50
Isotonic injection/infusion	1.39

POLYETHYLENEOXIDE[72]

Non proprietary name	**:**	USPNF : Polyethyleneoxide
Synonyms	:	Polyox ; polyoxirane ; polyoxyethylene
Chemical name	:	Polyethylene oxide
Empirical formula	:	CH_2CH_2O
Description	:	White to off white, free flowing powder, slight ammonical odour.
Structural formula	**:**	$(CH_2CH_2O)_n$
Functional category	**:**	Mucoadhesive , thickening agent, tablet binder.
Melting point	**:**	65 – 70^oC
Applications	**:**	Polyethylene oxide can be used as a tabler binder at a concentration of 5-85%. It has been shown to be an excellent mucoadhesive polymer. The film form of PEO demonstrate good lubricity when wet.It also acts as a radiation crosslinked in solution to poduce a hydrogel that can be used in wound care application.
Stability and storage conditions	**:**	Store in tightly sealed containetr in a cool, dry place. Avoid exposure to high temperatre since this can result in reduction of viscosity.

CARBOXYMETHYLCELLULOSE SODIUM[73]

Nonpropietary names	**:**	BP: Carmellose sodium JP : Carmellose sodium PhEur : Carmellose natricum USP : Carboxymethylcellulose sodium
Synonyms	**:**	Akucell, aquasorb, blanose, cellulose gum, SCMC finnifix, tylose CB, nymcel, sodium cellulose glycolate, sodium carboxymethylcellulose.
Chemical name and CAS Registry number	**:**	Cellulose, carboxymethyl ether, sodium salt [9004-32-4]
Emperical formula and Molecular weight	**:**	The USP 28 describes carboxymethylcellulose sodium as the sodium salt of polycarboxymethyl ether of cellulose. Typical molecular weight is 90000-7000000 g/mol.
Functional category	**:**	Coating agent, stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity increasing agent, wet absorbing agent.
Description	**:**	Carboxymethylcellulose sodium occurs as a White to almost white, odorless, granular powder.
Melting point	**:**	Browns at approximately 227^{o}C and chars at Approximately 252^{o}C.

Applications	**:**	Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing property. It may also be used as a tablet binder and disintegrant and to stabilize emulsions. higher concentrations usually 3-6% of the medium viscosity grade are used to produce gels that can be used to produce gels that can be used as the base for application and pastes. It is additionally one of the main ingredient of self-adhesive ostomy, wound care and dermatological patches where it is used as muco adhesive and to absorb wound exudates or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post surgical tissue adhesions. It is also used in cosmetics, toiletries, surgical prosthetics and incontinence, personel hygiene and food products.
Stability and storage Conditions	**:**	It is stable, though hygroscopic material. Under high humidity, it can absorb a large quantity of water. In tablets, this has been associated with decrease in tablet hardeness and increase in disintegration time. Aqueous solution are stable at

p^H 2-10 ; precipitation can occur below p^H 2..This results in significant decrease in viscosity, deterioration in the properties of solution prepared

from the sterilized material. Aqueous solution stored for prolonged periods should contain an antimicrobial preservative. Bulk material should be stored in a well closed container in a cool, dry place.

MICROCRYSTALLINE CELLULOSE[74]

Non proprietary names	**:**	BP : Microcrystalline cellulose JP : Microcystalline cellulose Ph Eur : Cellulose microcristallinum USPNF : Microcrystalline cellulose
Synonyms	**:**	Cellulose gel, crystalline cellulose , fibrocel , tabalose.
Chemical name and CAS Registry number	**:**	Cellulose [9004-34-6]
Emperical formula and Molecular weight	**:**	$(C_6H_{10}O_5)_n$ ~ 3600 where n ~ 220
Functional category	**:**	Adsorbent, suspending agent, tablet and capsule Diluents, tablet disintegrant.
Description	**:**	Microcrystalline cellulose is purified, partially

depolymerised cellulose that occurs as a white, odourless tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades that have different properties and applications.

Melting point : Chars at 260-270^{o} C

Applications : Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder / diluents in oral tablets and capsule formulation where it is used in both wet granulation and direct compression process. In addition it also has some lubrication and disintegrant properties that makes it useful in tableting.

Stability and storage Conditions : It is stable through hygroscopic materials. The bulk material should be stored in a well – closed container in a cool, dry place.

COPOVIDONE[75]

Nonpropietary name	**:**	BP : Copovidone PhEur : Copovidone USP –NF :Copovidone
Synonyms	**:**	Acetylacid vinyl ester , plasidone S – 630, PVP /VA copolymer , PVP/VA , polyvinylpyrr -olidone – vinyl acetate copolymer.
Chemical name and CAS	**:**	Acetic acid ethynyl ester , polymer with
Registry number		1-ethynl-2-pyrrolidone [25086-89-9]
Empirical formula and	**:**	$(C_6H_9NO)_n$ $(C_4H_6O_2)_m$
Molecular formula		
Functional category	**:**	Film-forming agent ; granulation aid; binder
Melting point	**:**	140^oC
Applications	**:**	Copovidone is used as a tablet binder, a filmformer and as a part of the matrix material used in controlled release formulation. In tableting, copovidone can used as a binder for direct compression and as a binder in wet granulation copovidone is often added to coating solution as a film-forming agent. It provides good adhesion, elasticity and hardnessand can be used as a moisture barrier.
Description	**:**	Copovidone is a white to yellowish amorphous powder. It is typically spray –dried with a

relatively fine particle size. It has a slight odour and a faint taste.

Stability and storage Conditions : Copovidone is stable and shold be stored in a well-closed container in a cool ,dry place.

AEROSIL[76]

Nonpropietary : BP : Colloidal anhydrous silica

JP : Light anhydrous silica acid

PhEur : Slica colloidal anhydrous

USP-NF : Colloidal silicon dioxide

Synonyms : Colloidal silica, fumed silica, fumed silicon dioxide**,** hochdisperses silicum dioxid, SAS, silicon dioxide colloidal.

Chemical name and CAS Registry number : Silica [7631-86-9]

Emperical formula and : Sio_2

Molecular weight : 60.08 g/mol

Functional category : Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.

Application : It is widely used in pharmaceutical, cosmetics and food products. Its small particles size and large

specific surface area give it desirable flow characteristics that are exploited to improve the flow property of dry powders in a number of processes such as tableting and capsule filling. It is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolids preparation In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling and minimize the clogging of spray nozzle. Colloidal is also used as a tablet disintegrant and as an absorbent dispencing agent for liquids in podwer. It is also used as an adsorbent during the preparation of wax microspheres as a thickening agent for topical preparation has been used to aid the freeze drying of nanoparticles and nanosphere suspensions.

Melting point **:** $1600^{o}C$

Description **:** It is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluishwhite coloured, odorless, tasteless, amorphous powder.

Stability and storage **:** It is hygroscopic but adsorbs large quantities of

Conditions water without liquifing. When used in aqueous system at a p^{H} 0-7.5, colloidal silicon dioxide is effective in increasing viscosity property of colloidal silicon dioxide are reduced ; and at p^{H} greater than 10.7 this ability is lost entirely since the silicate dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well closed container.

MAGNESIUM STEARATE[77]

Non proprietary name	*:*	BP: magnesium stearate, JP: magnesium stearate, Pheur: magnesii stearas, USPNF: magnesium stearate.
Synonyms	*:*	Magnesium octsdecanoate; octa decanoic acid,magnesium salt; stearic acid, magnesium salt
Chemical name and CAS registry number	*:*	Octadecanoic acid magnesium salt [557-04-0]
Functional category	*:*	Tablet and capsule lubricant
Application in pharmaceutical formulation or technology	*:*	Magnesium stearate is widely used in cosmetics, foods and in pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture.
Description	*:*	Magnesium stearate is a very fine, light white, precipitated or milld, implantable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greesy to the touch and readily adheres to the skin.
Melting range	*:*	117-150^{o}C (commercial samples); 126-130^{o}C (high purity magnesium stearate)

LACTOSE[78]:

Nonproprietary names : Lactose (BP), Lactose Monohydrate (PhEUR, USP-NF).

Synonym : CapsuLac, GranuLac, Lactochem, lactosum monohydricum, onohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 30GR, Tablettose.

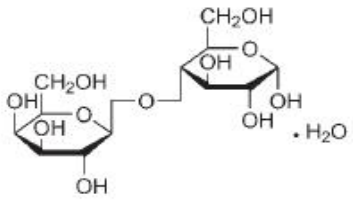
Chemical Name and

CAS Registry Number : O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate, [10039-26-6]

Emprical Formula and

molecular weight : Formula:$C_{12}H_{22}O_{11}\cdot H_2O$. MW: 360.31

Description : In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. αlactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting.



pH : 5.5-8.9.(1%w/w aqueous solution at 25^o)

Solubility	**:**	Insoluble in chloroform, ethanol, ether. Soluble in water in ratio of 1 in 5.24.
Melting point monohydrate)	**:**	201–202^{0}C (for dehydrated a-lactose
Moisture content	**:**	Lactose monohydrate contains normally has a range of 4.5 – 5.5% w/w water content.
Functional Category	**:**	Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.
Applications	**:**	Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.
Incompatibilities	:	A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

Stability and storage conditions : Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Chapter VI

Materials and Methods

MATERIALS AND METHODS

MATERIALS:

Drug : Gabapentin was obtained from Torrent Pharmaceuticals, Ltd.

Table 6: List of materials

S.NO.	MATERIALS	SUPPLIER
1	Gabapentin	Torrent Pharmaceuticals, Ltd
2	HPMC K100M	ISP, Hyderabad
3	Sodium bicarbonate	Merck Specialities Pvt. Ltd
4	Poly ethylene oxide	Merck Specialities Pvt. Ltd
5	Sodium CMC	ISP, Hyderabad
6	Micro crystalline cellulose	Dr. Reddy's Lab ,Hyderabad
7	Poly vinyl pyrollidine	ISP, Hyderabad
8	Aerosil	S.D Fine Chemicals, Mumbai

EQUIPMENTS :

Table 7: Equipments used and their manufacturers

S.NO	INSTRUMENTS	MANUFACTURES/ SUPPLIERS
1	Electronic Balance	ER-200A(AFCOSET)
2	Punching machine	RIMEK 10 station compression machine
3	Hardness Tester	Pfazer [Ssi-62(B)]
4	Friability Test Apparatus	Roche Friabilator
5	Tap density tester	Electro lab
6	pH meter	ELICO LI 120 P^H Meter
7	Tablet Dissolution Tester (USP Π)	ELECTROLAB (TDT-O8L)
8	HPLC	WATERS 2487 DUAL ABSORBANCE DETECTOR.
9	FTIR Spectrophotometer	BRUKER IR instrument
10	Mesh # 25, 40, 60	Retsec (ASLOO)

METHODOLOGY :

To formulate an intelligent formulation, the pre-formulation studies are usually the quantitative assessment of chemical stability of drug as well as stability in presence of other excipients for a formulation.

a) PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study[79].

The following Preformulation studies were performed:

- Study of organoleptic properties
- Solubility analysis
- Melting point of drug
- Drug powder characterization
- Particle size analysis
- Physical compatibility studies
- Identification of drug-excipients compatibility study by FT-IR

Organoleptic properties:

Colour: a small quantity of pure gabapentin powder was taken in a paper and viewed in well illuminated place.

Taste and odour: Very less quantity of gabapentin was used to get taste with the help of tongue as well as smelled to get the odour.

Loss on drying:

Determine on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Accurately weigh the substance to be tested. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm. Place the loaded bottle in the drying chamber. Dry the sample at the specified temperature from constant weight[80]. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

Solubility analysis[81]:

Solubility is important pre-formulation parameter because it affects the dissolution of drug, bioavailability of drug.

Method: weigh appropriate quantity of drug and added to the suitable volume of solvent.

Melting point:

The melting point of gabapentin was determined by capillary method, using small quantity of gabapentin was taken and placed in apparatus and determined the melting point and matched with standards[82].

Drug powder characterization:

Angle of repose[83]: The frictional forces in a loose powder or granules can be measured by angle of repose. This is themaximum angle possible between the surface of a pile of powder or granules and the horizontal plane and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface[82]. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table-8: Limits:

Angle of repose	**Flow property**
$<25^{o}$	Excellent
$25\text{-}30^{o}$	Good
$30\text{-}40^{o}$	Passable
$>40^{o}$	Very poor

Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more

spherical in shape, bulk density is increase. In addition as the granule size increases bulk density decreases.

Method: weighed quantity of active powder ingredient (API) was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by the API was measured. Bulk density was measured by using the formula

Bulk Density = Bulk Mass / Bulk Volume

Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes is observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance. Device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Cylinder dropping distance: 14± 2mm at a normal rate of 300 drops / minute.

Unless otherwise specified, tab the cylinder 500 times initially and measure the tapped volume Va, the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

$$\textbf{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm, Vf = volume of material after tapping.

Generally replicate determinations are desirable for the determination of this property.

Measurement of Powder Compressibility:

The compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing power, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner Ratio Calculated by the formula:

$$\textbf{Compressibility index:} = 100\frac{(V_0 - Vf)}{V_0}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table : 9 Limits

S.no	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

$$\textbf{Hausner Ratio:} = \frac{V_0}{Vf}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table-10: Limits:

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

Physical compatibility studies[84]:

In the tablet dosage form the drug is in intimate contact with one or more excipients, the latter could affect the stability of the drug. Knowledge of drug excipient interactions, therefore very useful to the formulator in selecting the appropriate excipients.

Gabapentin was mixed well with the excipients according to the formula selected for the tabletting and kept small portion of this mixed powder in cleaned and dried vials in stability chamber at $40^{o}C\pm2^{o}$ C / 75±5RH and room temperature. Physical observations have been carried out visually for 7 days.

a) **COMPATIBILITY STUDIES:**

One of the requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FTIR spectrometer to find out if, any possible chemical interaction of Gabapentin with HPMC K100M , Sodium CMC, PEO. Compatibility with polymers was confirmed by FTIR studies.

FOURIER TRANSFORMS INFRARED SPECTROMETRY (FTIR):

Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (FTIR) using Bruker spectrometer model[85]. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:200. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

c)PREPARATION OF STANDARD CALIBRATION CURVE OF GABAPENTIN:

METHOD:

Gabapentin is estimated chromatogramically in HPLC at 210 nm.

PREPARATION OF PH 6.9 BUFFER SOLUTION[86]:

7gms of Potassium dihydrogen orthophosphate was weighed and taken in 1000 ml beaker. It is been dissolved and diluted with 1000 ml of HPLC water. And now this solution has been adjusted to PH 6.9 with KOH.

PREPARATION OF MOBILE PHASE:

940ml (94%) of above prepared buffer solution is been mixed up with 60 ml (6%) of Acetonitrile HPLC and was degassed in ultrasonic water bath for 5 mins and this solution is been filtered through 0.45µ filter under vacuum filtration

PREPARATION OF STANDARD DRUG SOLUTION:

STANDARD SOLUTION:

2 ml of stock solution is taken and this is made up to 20 ml with the mobile phase. 100ppm concentration of solution is prepared. From these different dilutions where prepared like 20ppm, 30ppm, 40ppm, 50ppm, 60ppm respectively with mobile phase used as diluent's solution. And peak areas of this solutions are been taken at 210 nm in HPLC .

FORMULATION OF GABAPENTIN FLOATING TABLETS:

Table : 11: Ingredients used and their role

S.NO.	MATERIALS	CATEGORY
1	GABAPENTIN	Active ingredient
2	SODIUM CMC	Polymer
3	PEO	Polymer
4	HPMC K100M	Polymer
5	PVP	Binder
6	MCC	Disintegrant
7	LACTOSE	Diluent
8	AEROSIL	Glidant
9	SODIUMBICARBONATE	Alkalizing agent
10	MAGNESIUM STERATE	Lubricant

Formulation of gabapentin floating tablets:

Table: 12 : Quantity of Raw Materials per Tablet (In mg)

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**
Gabapentin	600	600	600	600	600	600	600	600	600
PEO	150	175	200	–	–	–	–	–	–
HPMC K100M	–	–	–	150	175	200	–	–	–
Sodium CMC	–	–	–	–	–	–	150	175	200
MCC	75	60	45	75	60	45	75	60	45
Lactose	30	20	10	30	20	10	30	20	10
PVP	50	50	50	50	50	50	50	50	50
Aerosil	10	10	10	10	10	10	10	10	10
Mg.stearate	10	10	10	10	10	10	10	10	10
$NaHCo_3$	25	25	25	25	25	25	25	25	25

FORMULATION PROCEDURE[87, 88]:

Direct compression method:

These formulations are prepared by direct compression technique.

The following steps were taken while preparation of Gabapentin floating tablets

1. In each formulation Gabapentin, HPMC K100M, and all ingredients were mixed and pass through 40#.
2. All the ingredients were mixed thoroughly by triturating up to 15 minutes.
3. The powder mixture was lubricated with magnesium stearte and also add aerosol.
4. The tablets were prepared by using direct compression method.

EVALUATION OF GABPENTIN FLOATING TABLETS:

Lubricated blends of all formulations was examined and determined Angle of repose, Loss on drying, Bulk density, tapped density, Carr's index and Hausner's ratio as procedure given in preformulation section. All observations are given in results and discussion section.

EVALUATION OF GABPENTIN FLOATING TABLETS:

a)TABLET DESCRIPTION[89]:

General appearance of tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or an odor, taste, surface texture, physical flaws and consistency and legibility of any identify markings.

b) TABLET DIMENSIONS:

Thickness and were measured using a calibrated vernier caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

c) HARDNESS:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined[88].

d) FRIABILITY TEST:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions[90]. The tablets were weighed again (w). The % friability was then calculated by

Percentage of Friability = $100\ (1-w/w_0)$

Percentage friability of tablets less than 1% is considered acceptable.

e) WEIGHT VARIATION TEST:

Twenty tablets were selected at random and the average weight was determined[91]. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage. USP official limits of percentage deviation of tablet are presented in the Table 13.

Table.13: Weight Variation Tolerances for Uncoated Tablets

S. NO.	AVERAGE WEIGHT OF TABLETS (mg)	MAXIMUM % DIFFERENCE ALLOWED
1.	130 or Less	10
2.	130 to 324	7.5
3.	More than 324	5.0

% Maximum positive deviation = (W_H –A/ A) x 100

% Minimum negative deviation = (A-W_L/ A) x 100

Where,

W_H = Highest weight in mg.

W_L = Lowest weight in mg.

A = Average weight of tablet in mg.

f) TEST FOR CONTENT UNIFORMITY:

Chromatographic conditions:

Equipment	:	High performance liquid chromatography equipped with Auto Sampler and DAD or UV detector.
Column	:	C18 (4.6 x 250mm, 5 µm, Make: chromatopak) or equivalent
Flow rate	:	1.2 ml per min
Wavelength	:	210 nm
Injection volume	:	20 µl
Column oven	:	Ambient
Run time	:	12 min

PREPARATION OF PH 6.9 BUFFER SOLUTION:

7gms of Potassium dihydrogen orthophosphate was weighed and taken in 1000 ml beaker. It is been dissolved and diluted with 1000 ml of HPLC water. And now this solution has been adjusted to PH 6.9 with KOH.

PREPARATION OF MOBILE PHASE:

940 ml (94%) of above prepared buffer solution is been mixed up with 60 ml (6%) of Acetonitrile HPLC and was degassed in ultrasonic water bath for 5 minutes.

And this solution is been filtered through 0.45µ filter under vaccum filtration.

STOCK SOLUTION:

100mg of Gabapentin was taken into a 100 ml volumetric flask and to it small amount of HPLC water (10 ml) is been added and is kept for sonication for the drug to get properly dissolved and after that it is made up to 100 ml with mobile phase which has been prepared before thus 1000 ppm concentration of stock solution is been prepared.

STANDARD SOLUTION:

2 ml of stock solution is taken and this is made up to 20 ml with the mobile phase. 100 ppm concentration of solution is prepared. From this 4 ml was taken and diluted to10 ml with mobile phase used as diluent's solution. And peak areas of the solution are taken at 210 nm in HPLC.

SAMPLE PREPARATION:

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to 100 mg of drug was taken and dissolved in 100 ml of mobile phase. And from that 2ml is taken and is diluted with 20 ml of mobile phase. Further take 4ml solution and make upto 1 0ml with mobile phase and is been kept in HPLC at 210 nm in order to obtain a peak area.

Procedure: Separately inject standard preparations and sample preparations, record the chromatograms, and measure the responses for analyte peaks. Calculate the quantity as % drug release.

Calculation:

Assay % =

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \frac{\text{Avg. Wt}}{\text{Label Claim}} \times 100$$

Where:

AT = Peak Area of Gabapentin obtained with test preparation

AS = Peak Area of Gabapentin obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

DT = Dilution of sample solution

P = Percentage purity of working standard

8.5 BUOYANCY / FLOATING TEST[92,93]:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The *In*

vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCL. The time required for the table to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time.

8.6 SWELLING STUDIES[94]:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900 ml of distilled water which was maintained at 37^{o} + 0.5^{o}C, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU)

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

***IN- VITRO* DRUG RELEASE STUDY:**

Dissolution Parameters:

Medium	: 0.1 N HCL.
Apparatus	: USP – Type II (Paddle).
RPM	: 100.
Temperature	: $37^{o}\pm 0.5^{0}$ C.
Medium Volume	: 900 ml

Chromatographic conditions:

Equipment	:	High performance liquid chromatography equipped with Auto Sampler and DAD or UV detector.
Column	:	C18 (4.6 x 250mm, 5 µm, Make: chromatopak) or equivalent
Flow rate	:	1.2 ml per min
Wavelength	:	210 nm
Injection volume	:	20 µl
Column oven	:	Ambient
Run time	:	12 min

Limits:

According to USP-29 Specification

At 1st hour	--	between 10-25%
At 9th hour	--	between 45-85%
At 12 thhour	--	no less than 70%

PREPARATION OF PH 6.9 BUFFER SOLUTION:

7gms of Potassium dihydrogen orthophosphate was weighed and taken in 1000 ml beaker. It is been dissolved and diluted with 1000 ml of HPLC water. And now this solution has been adjusted to PH 6.9 with KOH.

PREPARATION OF MOBILE PHASE:

940 ml (94%) of above prepared buffer solution is been mixed up with 60 ml (6%) of Acetonitrile HPLC and was degassed in ultrasonic water bath for 5 minutes. And this solution is been filtered through 0.45µ filter under vaccum filtration.

PREPARATION OF STANDARD DRUG SOLUTION:

Stock solution:

100mg of Gabapentin was taken into a 100 ml volumetric flask and to it small amount of HPLC water (10 ml) is been added and is kept for sonication for the drug to get properly dissolved and after that it is made up to 100 ml with mobile phase which has been prepared before thus 1000 ppm concentration of stock solution is been prepared.

STANDARD SOLUTION:

2 ml of stock solution is taken and this is made up to 20 ml with the mobile phase. 100 ppm concentration of solution is prepared. From these different dilutions where prepared like 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml, 60µg/ml respectively with mobile phase used as diluent's solution. And peak areas of this solutions are been taken at 210 nm in HPLC.

SAMPLE PREPARATION:

Set the dissolution parameters as mentioned above. Place the formulated tablets in dissolution vessels and operate the apparatus for specified time. At the end of the specified time, with draw about 5 ml of the solution from a zone mid way between the dissolution medium and the top of the rotating basket, not less than 1cm from then vessel wall

Procedure:

In-vitro release studies were carried out using USP Type 1 apparatus (rotating basket). 900 ml of 0.1 N HCl was taken in dissolution vessel and the temperature of the medium was maintained at $37^0C \pm 0.5^0C$. The speed was 100 rpm. 5ml of sample was withdrawn at pre-determined time intervals and same volume of fresh medium was replaced. The samples are filtered with 0.45 filter medium. And the samples are loaded in HPLC and record the chromatograms and measure the responses for analytic peaks. Calculate the quantity as % drug release.

Calculations

% of drug release:

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{900}{WT} \times \frac{P}{100} \times 100$$

AT = Peak Area of Gabapentin obtained with test preparation

AS = Peak Area of Gabapentin obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

P = Percentage purity of working standard

KINETIC DATA ANALYSIS [95,96]

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero - order kinetic model - Cumulative % drug released versus time.
2. First – order kinetic model - Log cumulative percent drug remaining versus time.
3. Higuchi's model - Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model - Log cumulative percent drug released versus log time.

1. Zero order kinetics:

Zero order release would be predicted by the following equation: -

$$A_t = A_0 - K_0 t$$

Where,

A_t = Drug release at time‘t’.

A_0 = Initial drug concentration.

K_0 = Zero - order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order equal to K_0.

2. First Order Kinetics:

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where,

C = Amount of drug remained at time‘s’.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with the slope values.

3. Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation:

$$Q = [D\varepsilon / \tau (2A - \varepsilon Cs) Cst]^{½}$$

Where,

Q = Amount of drug released at time's'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs' and 'A' are constant. Then equation becomes: -

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the floating tablets of Gabapentin, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behavior from polymeric systems

DIFFUSION COEFFICIENT:

From the Korsemeyer peppas equation, diffusion coefficient is determined using the equation

$$\mathbf{M_t/M_\infty = kt^n}$$

Where, Mt/M∞ represents the fraction of drug release at time t, k is the release rate constant and n is the diffusion coefficient.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table14, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Table : 14 Limits

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

STABILITY STUDIES[97]:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. And to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were Accelerated condition (40°C±2°C/75%RH). Stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in humidity chamber for 90 days on above mention temperature.

The following tests are performed after 90 days.

Tests performed:

- Drug content
- Dissolution profile
- Test for other physical parameters (hardness, weight variation, friability).

Chapter VII

Results and Discussion

RESULTS AND DISCUSSION

PREFORMULATION STUDY

a)Identification of drug and drug-polymer compatibility study

FTIR studies

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). No peaks are observed which interfere with the main drug peaks. The following spectrum and table shows IR spectrum for drug and polymer and the wave number of characteristic bands for the same.

The IR Spectrum preview pictures are as follows:

Figure 18 : FTIR Spectra of gabapentin

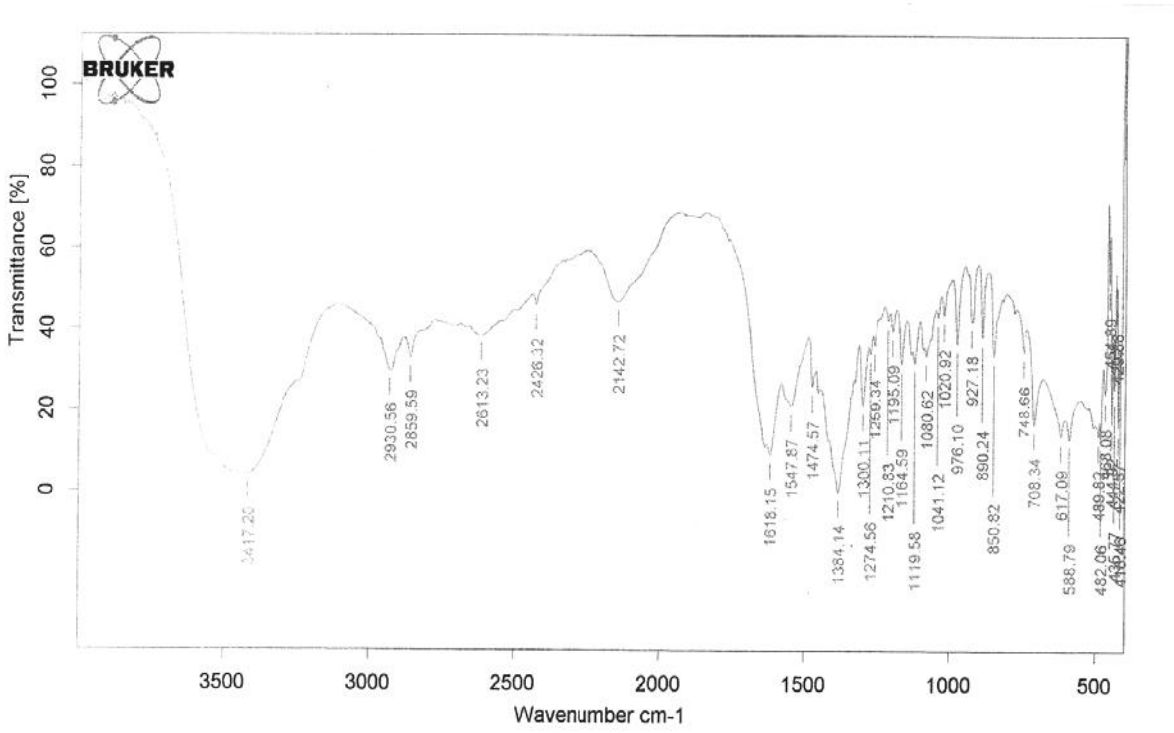


Table 16 : FTIR peak areas of gabapentin

S.No	Observed Frequency	Reported Frequency (cm-1)	Functional group(cm-1)
1	3417.20	3500-3300	N-H
2	2930.56,2859.59	2960-2850	C-H
3	2613.23,2426.32	2800-2340	OH
4	2142.72	2100-2200	C≡C

Figure 19 : FTIR Spectra of Sodium Carboxy methyl Cellulose

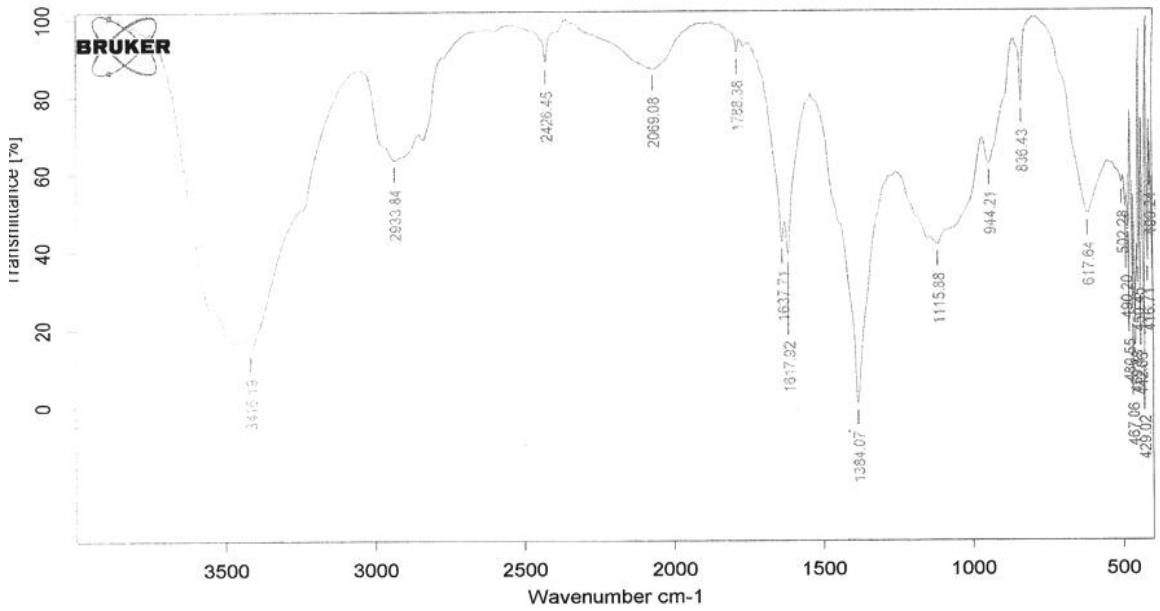


Table 17 : FTIR peak areas of Sodium Carboxy methyl cellulose

S.No	Observed Frequency	Reported Frequency (cm-1)	Reported Frequency (cm-1)
1	3416.19	3500-3300	N-H
2	2933.84	2960-2850	C-H
3	2426.45	2800-2340	OH
4	1617.92	1680-1630	C=O
5	1115.88	1200-1025	C-N

Figure 20 :FTIR Spectra of Polyethylene Oxide

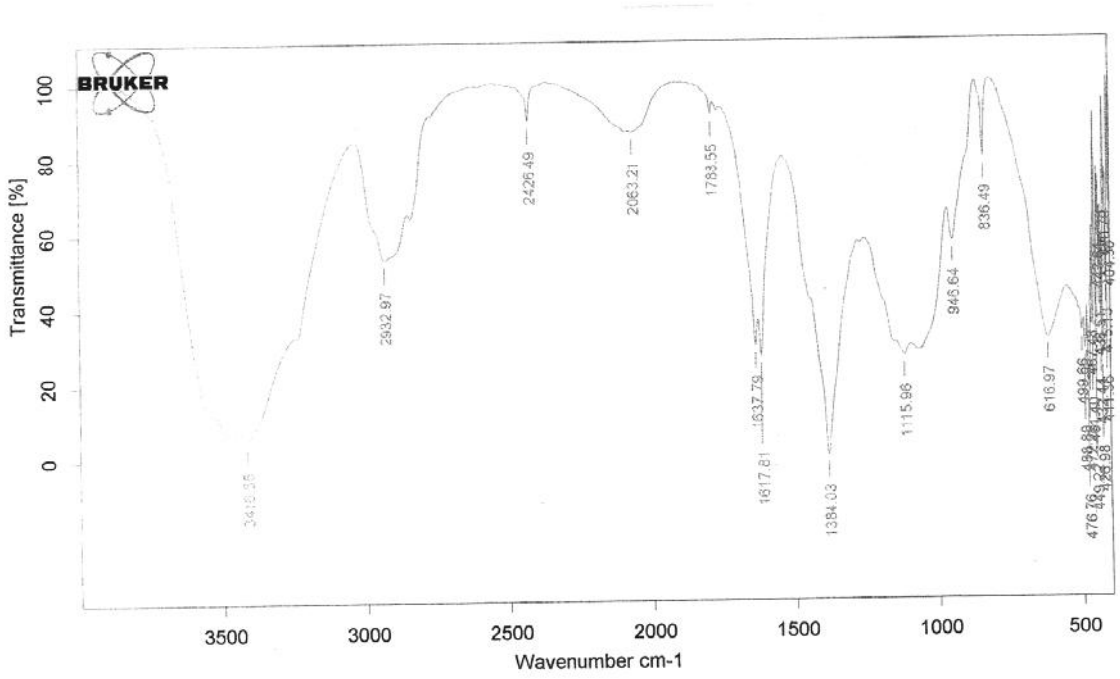


Table 18 : FTIR peak areas of Polyethylene Oxide

S.No	Observed Frequency	Reported Frequency (cm-1)	Reported Frequency (cm-1)
1	3416.55	3500-3300	N-H
2	2932.97	2960-2850	C-H
3	2426.49	2800-2340	OH
4	1617.81	1680-1630	C=O
5	1115.96	1200-1025	C-N

Figure 21:FTIR Spectra of HPMC K100M

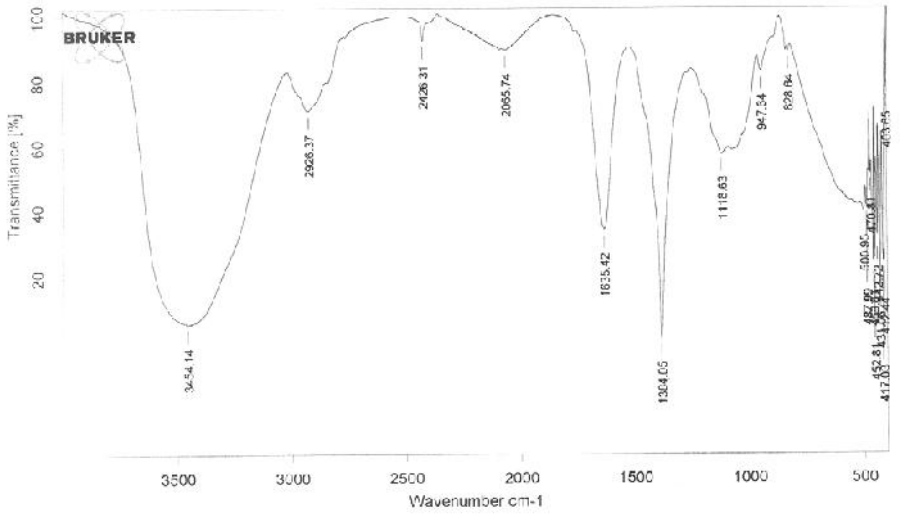


Table 19 :FTIR peak areas of HPMC K100M

S.No	Observed Frequency	Reported Frequency (cm-1)	Reported Frequency (cm-1)
1	3454.14	3500-3300	N-H
2	2926.37	2960-2850	C-H
3	2426.31	2800-2340	OH
4	1635.42	1680-1630	C=O
5	1384.05	1310-1410	C-O
6	1118.63	1200-1025	C-N

Figure 22 : FTIR Spectra of Gabapentin, polymers and excipients

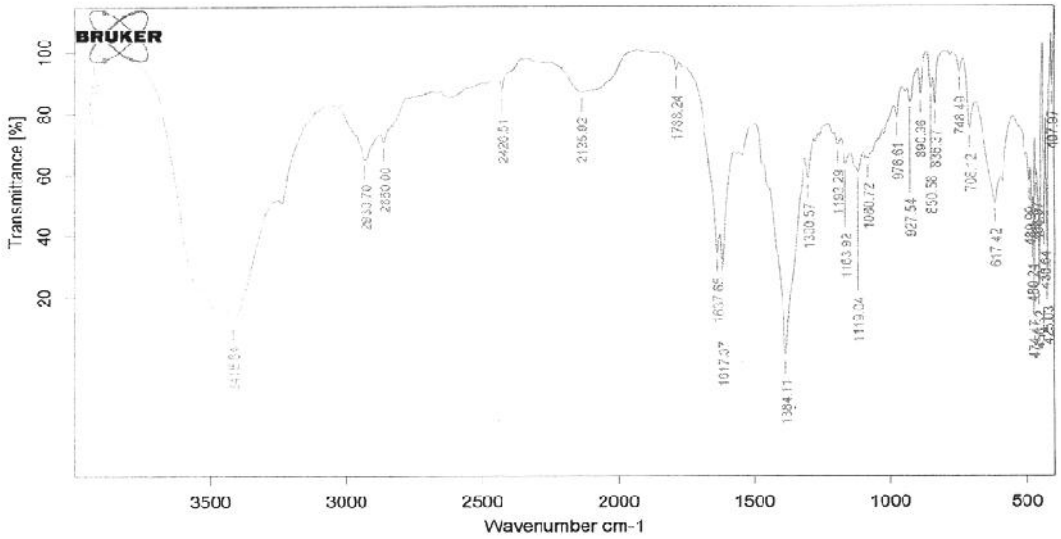


Table 20 : FTIR peak areas of gabapentin+polymers+excipients

S.No	Observed Frequency	Reported Frequency (cm-1)	Reported Frequency (cm-1)
1	34515.64	3500-3300	N-H
2	2930.70	2960-2850	C-H
3	2428.51	2800-2340	OH
4	1637.65	1680-1630	C=O
5	1384.11	1310-1410	C-O
6	1193.29	1200-1025	C-N

a) Melting point of drug

The melting point of gabapentin was determined by capillary method, melting point of gabapentin was found to be 162-166^{o}C **.** Melting point compared with USP standards that showed that drug is pure.

b) Solubility analysis

Gabapentin samples are examined and it was found to be soluble in water and slightly soluble methanol, dimethyl formamide. It also dissolves in dilute alkali and in dilute acids.

a) **POWDER CHARACTERIZATION:**

Table 21 : Observation of organoleptic properties of gabapentin

TEST	SPECIFICATION	OBSERVATION
Colour	White or almost white powder	White powder
Odour	---	Odourless

i) Angle of repose

It was determined as per procedure given in material and methodology section.

Table 22 : Determinations of Angle of repose of Gabapentin

Material	Angle of repose
Gabapentin Raw material	27°25"

The results indicating that the raw material has good flow property.

ii) Loss of Drying

It was determined as per procedure given in methodology. The results are as follows

Table 23 : Observations for loss on drying of Gabapentin

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.31%

The loss drying of drug was founded as 0.31 which is with in the limit.

iii) Flow properties

The method to determine the flow properties are given in methodology

.

Table 24 : Flow properties of pure drug Gabapentin

Material	Bulk density	Tapped density	Carr's index (%)	Hausner ratio (%)
Gabapentin raw material	0.21	0.34	10.52	1.104

The results are clearly indicating that the gabapentin raw material has free flow .

iv)Physical compatibility test

The method for determination of physical compatibility test was given in methodology.

Table 25 : Observation for physical compatibility test

Test	Observation	Inference
Description	No colour change was observed	Complies with the condition

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Table 26: Standard curve of Gabapentin

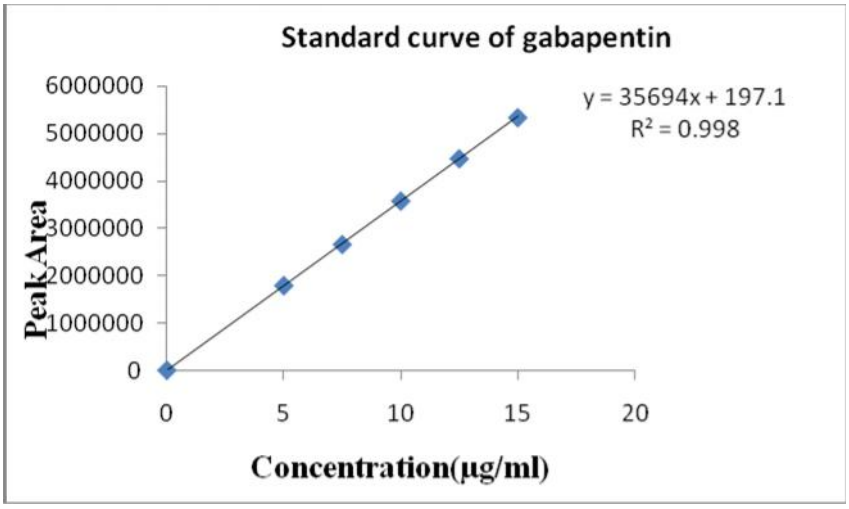
S.NO	Concentration (µg/ml)	Average peak area
01	20	1789722
02	30	2660326
03	40	3579445
04	50	4475206
05	60	5343689

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

$$Y = mx + c$$

Where Y=absorbance, m=slope, x=concentration

Figure 23 : Standard curve of Gabapentin



EVALUATION OF POWDER CHARACTERISTICS :

Table 27 : Evaluation of powder characteristics of F1-F9 Formulations

Formulation code	Angle of repose (degree± SD)	Bulk Density (gm/ml±SD)	Tapped Density (gm/ml±SD)	Carr's index (%± SD)	Hausner ratio (%± SD)
F1	26.42±0.04	0.311±0.02	0.337±0.02	14.35±0.06	1.03±0.05
F2	27.17±0.01	0.325±0.04	0.359±0.04	15.61±0.07	1.23±0.04
F3	29.01±0.03	0.339±0.06	0.361±0.07	14.64±0.04	1.14±0.02
F4	27.57±0.07	0.307±0.04	0.317±0.06	13.46±0.01	1.13±0.06
F5	26.77±0.09	0.287±0.03	0.321±0.05	12.29±0.05	1.25±0.03
F6	25.61±0.06	0.271±0.01	0.345±0.01	16.35±0.03	1.15±0.01
F7	26.16±0.03	0.297±0.04	0.357±0.03	14.46±0.07	1.20±0.03
F8	29.11±0.09	0.307±0.05	0.366±0.02	15.61±0.04	1.19±0.05
F9	28.05±0.02	0.320±0.06	0.359±0.04	13.85±0.09	1.21±0.00

The powders were evaluated for various flow properties. The powders of all batches showed good flow properties evident from the results shown in table-27. The angle of repose values were ranged from 25.61±0.06to 29.11±0.09. The results were found to be below 30; hence they have good flow ability. The Carr's index value ranged from 12.29±0.05to 16.35±0.03 and Hausner's ratio value ranged from 1.03±0.05to 1.25±0.03 hence they have good flow and free flow ability.

Table 28 : Physical Evaluation of formulated tablets

Formulation code	Weight variation (n=20) (mg ± SD)	Hardness (kg/cm^2±SD)	Friability (%)	Drug content (%± SD)	Thickness (%± SD)
F1	952±0.29	6.6±0.1	0.69	99.13±0.04	5.2±0.007
F2	951±0.67	6.4±0.2	0.67	98.19±0.01	5.3±0.006
F3	949±0.45	7.0±0.3	0.74	99.29±0.12	5.2±0.011
F4	951±0.71	6.7±0.5	0.71	98.19±0.09	5.3±0.008
F5	948±0.15	7.2±0.2	0.65	99.17±0.07	5.2±0.009
F6	952±0.31	6.8±0.4	0.63	98.61±0.03	5.2±0.013
F7	949±0.04	6.5±0.3	0.76	99.13±0.17	5.3±0.004
F8	948±0.71	7.3±0.3	0.70	99.11±0.14	5.2±0.012
F9	951±0.52	7.4±0.5	0.68	98.21±0.05	5.3±0.05

The formulated sustained release matrix tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 948±0.71to 952±0.29. The hardness of the prepared tablets was ranged from 6.4±0.2 to 7.4±0.3, friability values were ranged from 0.63 to 0.76. Drug content of tablets was ranged from 98.11±0.03 to 99.91±0.14, thickness of tablets was uniform and values are ranged from 5.2±0.013to 5.3±0.006.

Table : 29 Floating time of gabapentin tablets

Formulation Code	Lag time (seconds)	Total floating Time (hours)
F1	69	>12
F2	56	>12
F3	60	>12
F4	70	>12
F5	59	>12
F6	50	>12
F7	65	>12
F8	74	>12
F9	68	>12

Table 30: Percentage swelling index of formulated tablets

Formulation Code	Percentage Swelling index				
	Time (hours)				
	1	**2**	**3**	**4**	**5**
F1	30.06	41.68	59.78	71.56	82.64
F2	32.45	46.65	62.54	78.58	89.09
F3	29.26	49.64	63.24	86.35	92.64
F4	25.98	42.82	64.68	79.04	88.97
F5	27.57	54.65	68.12	80.5	92.36
F6	29.34	57.68	73.56	84.75	97.51
F7	28.00	41.76	50.99	71.24	86.29
F8	30.11	44.38	58.49	77.63	90.23
F9	26.16	49.25	64.21	81.87	94.19

The swelling behaviors all formulated tablets were calculated and results were ranging from 25.98 to 97.51. The results are clearly indicating that swelling capacity increases by increasing polymer concentration.

Figure 24: Percentage swelling index plot of F1-F3

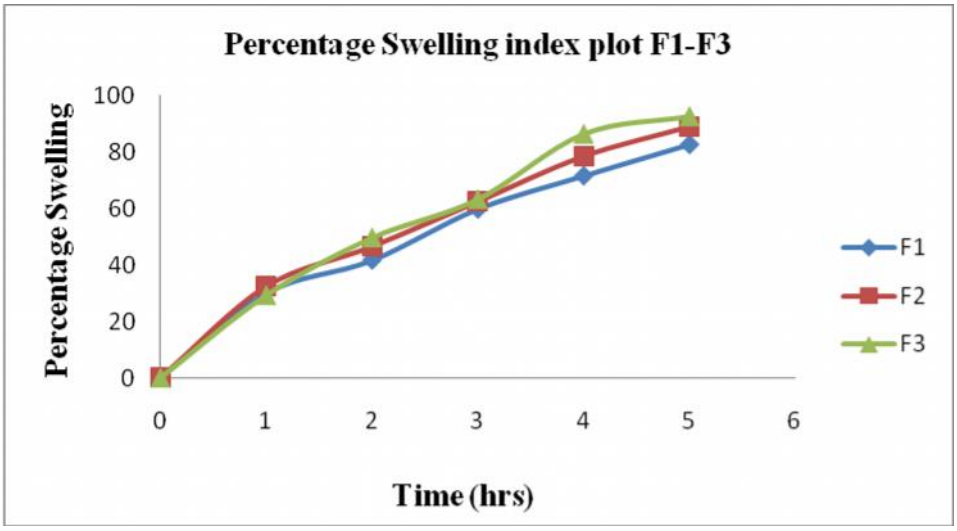


Figure 25: Percentage swelling index plot of F4-F6

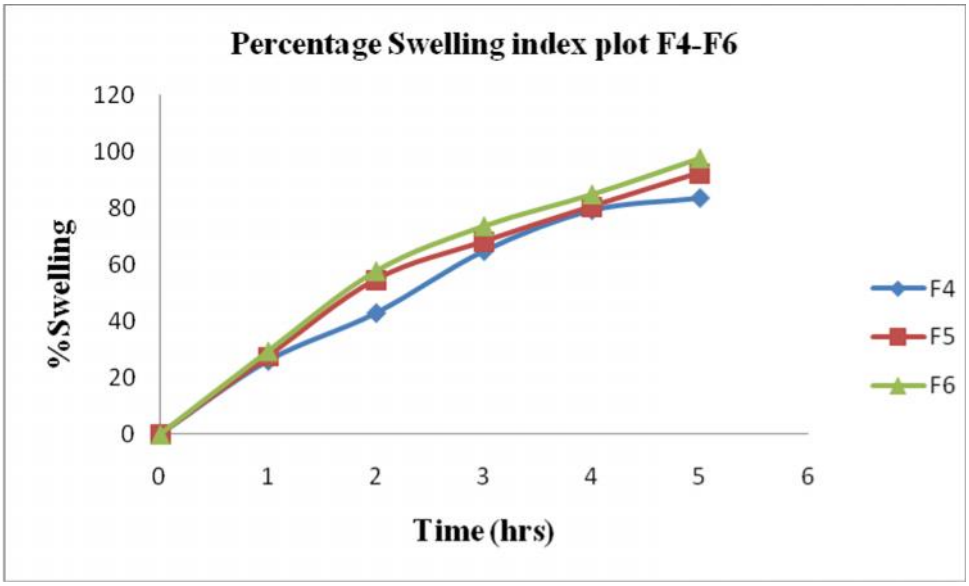


Figure 26: Percentage swelling index plot of F7-F9

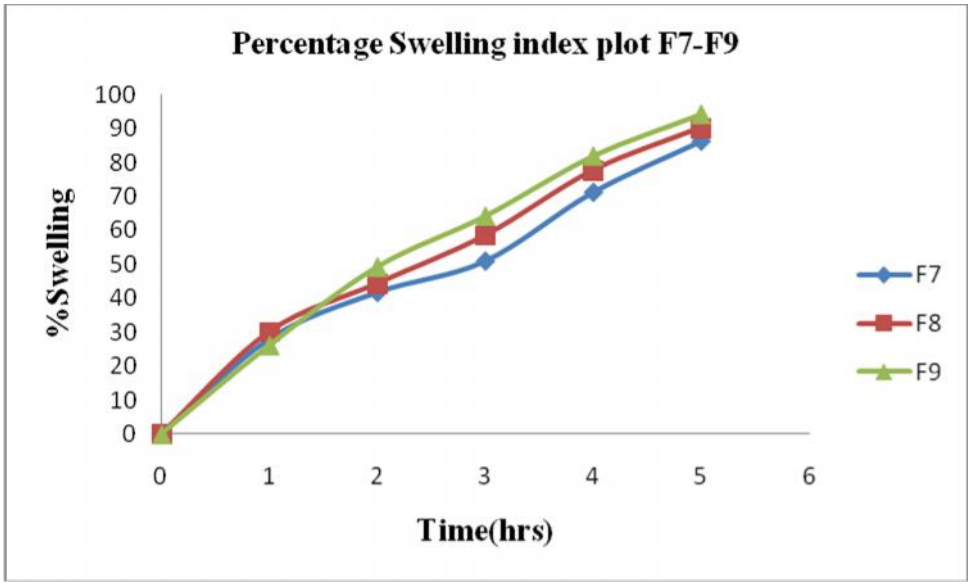


Table 31: *Invitro* drug release study of formulated sustained release formulations

TIME (hours)	CUMULATIVE PERCENT DRUG RELEASE (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	33.25	27.46	21.31	35.33	24.96	21.32	30.66	25.57	24.82
2	50.68	44.74	32.64	51.24	46.76	32.17	48.45	49.68	38.95
4	75.62	62.10	58.21	79.11	59.47	59.09	72.04	65.49	52.14
6	82.51	84.45	64.54	92.21	86.88	66.70	89.34	78.64	76.31
8	98.25	93.48	78.90	98.98	92.36	85.68	99.69	91.45	88.49
10	-	98.38	84.41	-	99.23	94.58	-	99.10	92.62
12	-	-	99.08	-	-	99.96	-	-	98.48

Figure 27: *Invitro* drug release of F1-F5

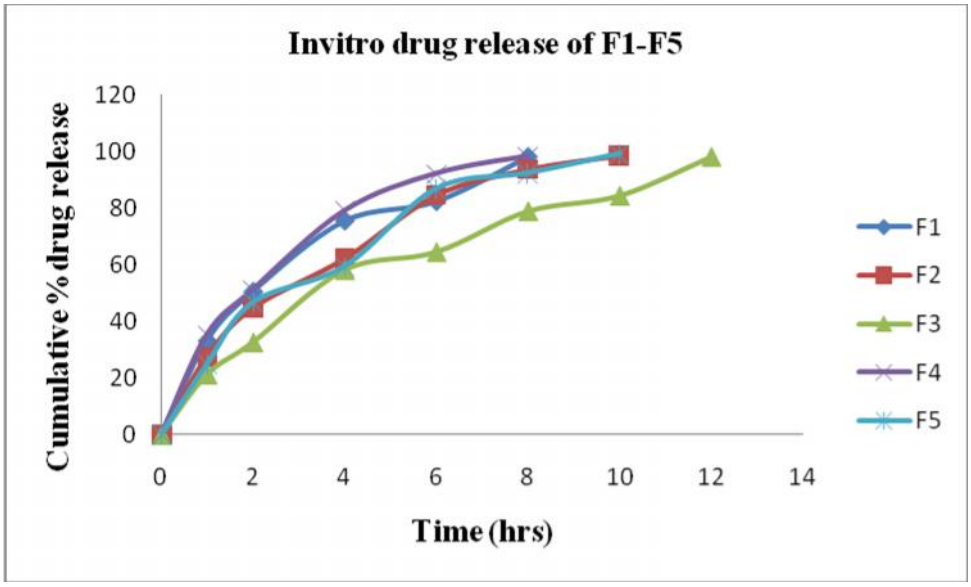


Figure 28: *Invitro* drug release of F6-F9

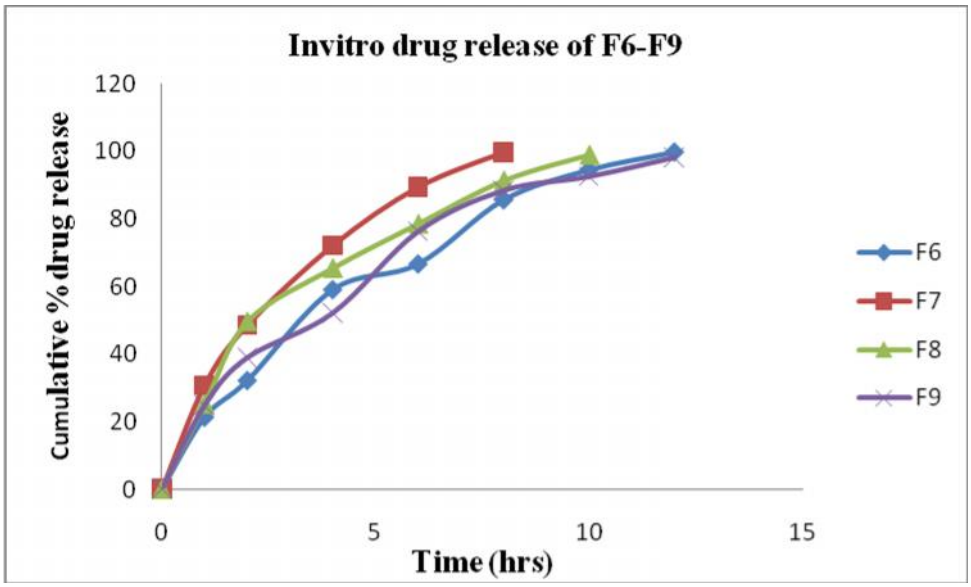


Figure 29: Standard peak of gabapentin optimum formulation

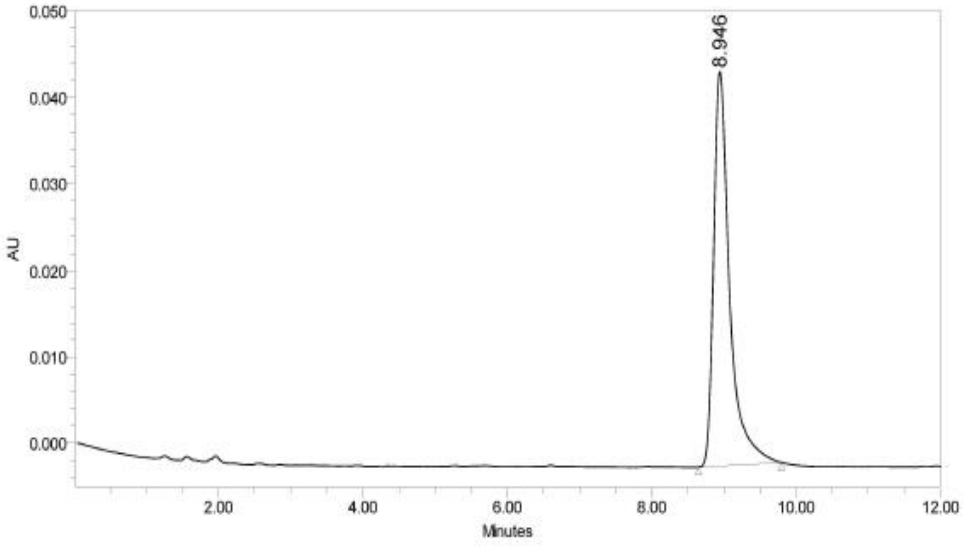


Figure 30: Peak obtained after 1hour dissolution

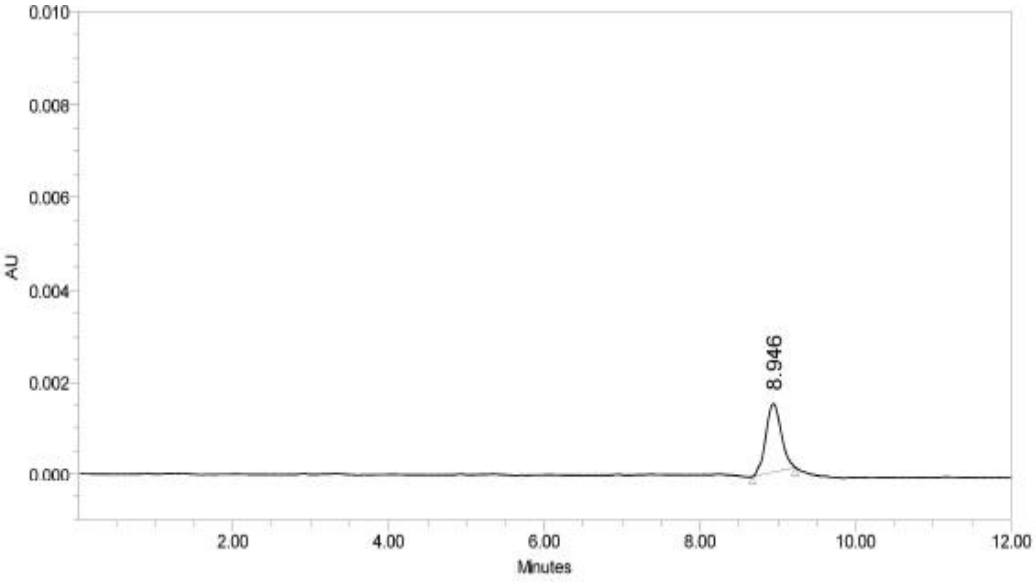


Figure 31: Peak obtained after 2 hours dissolution

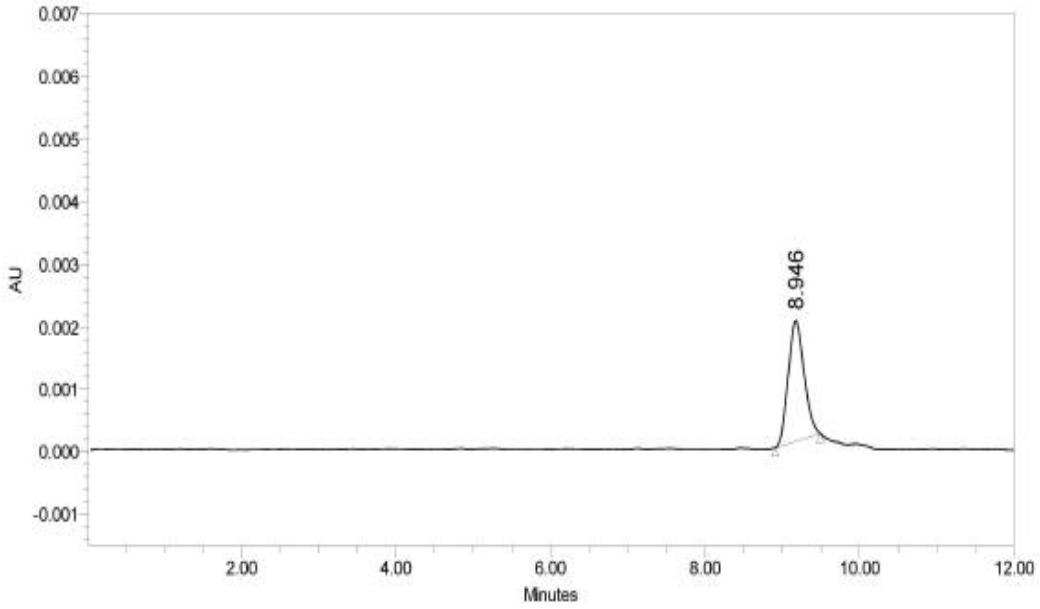


Figure 32: Peak obtained after 4 hours dissolution

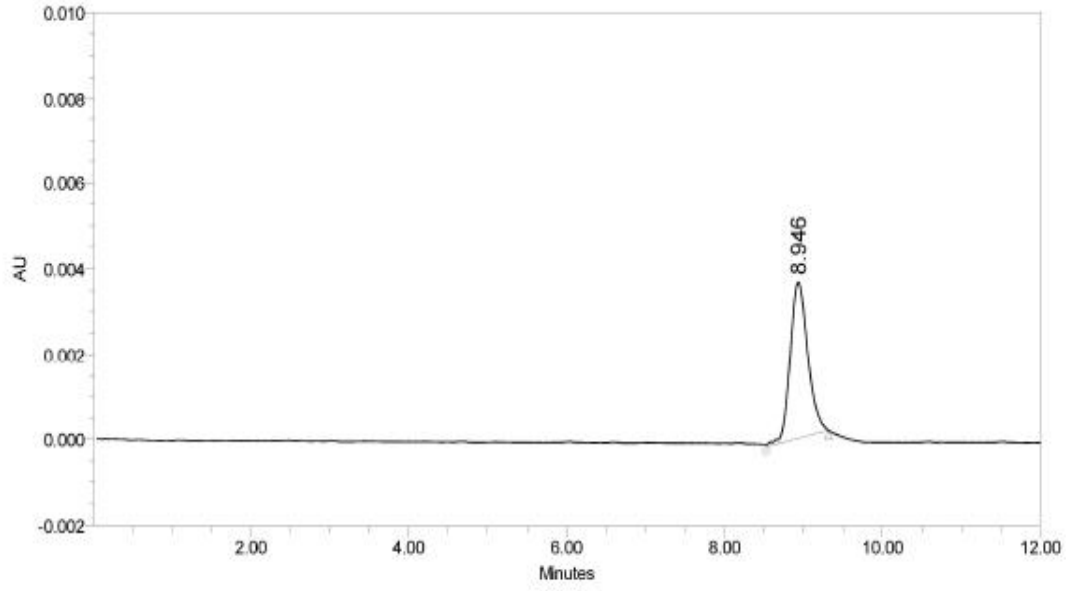


Figure 33: Peak obtained after 6 hours dissolution

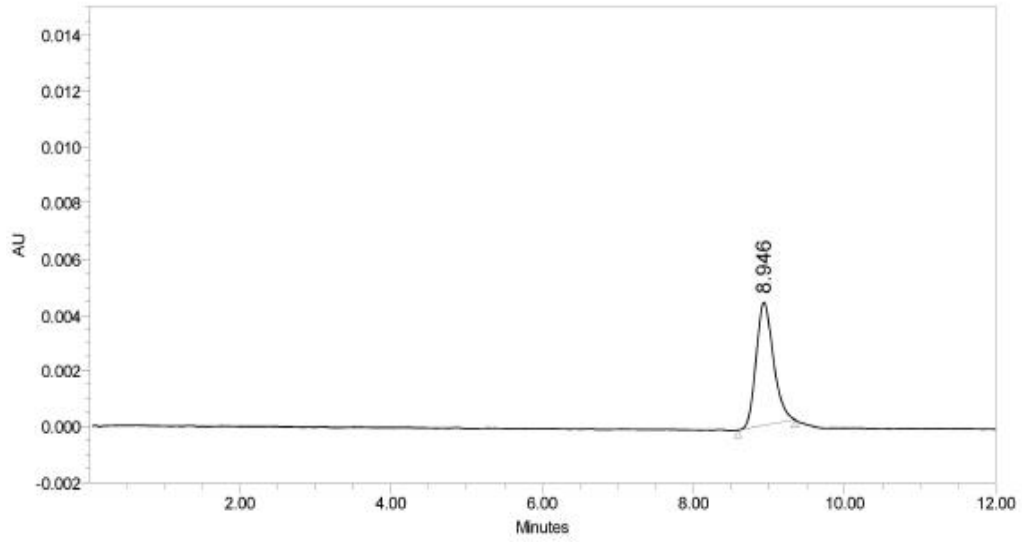


Figure 34: Peak obtained after 8 hours dissoluton

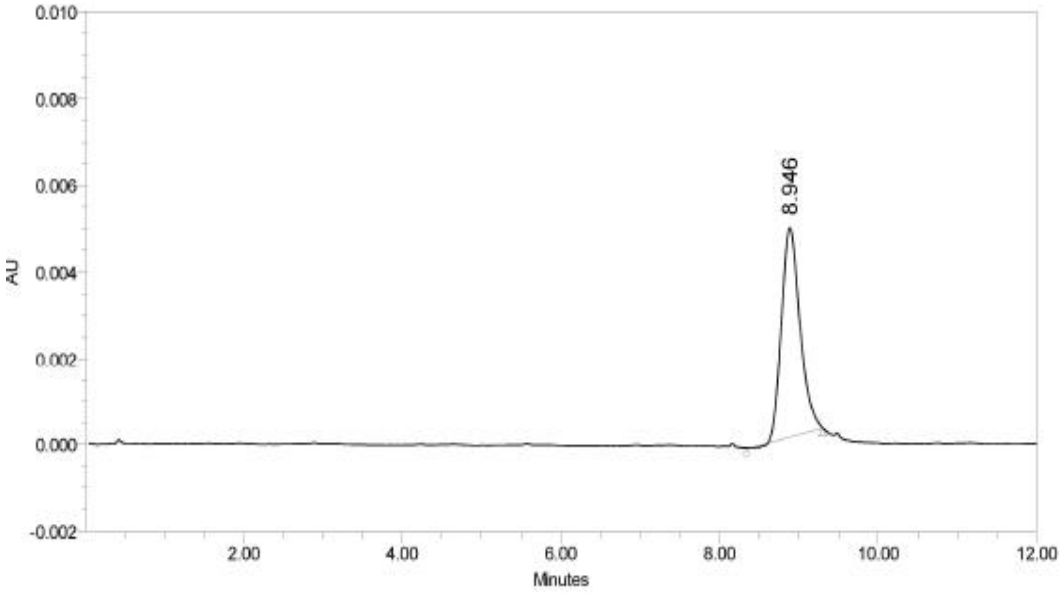


Figure 35: Peak obtained after 10 hours dissolution

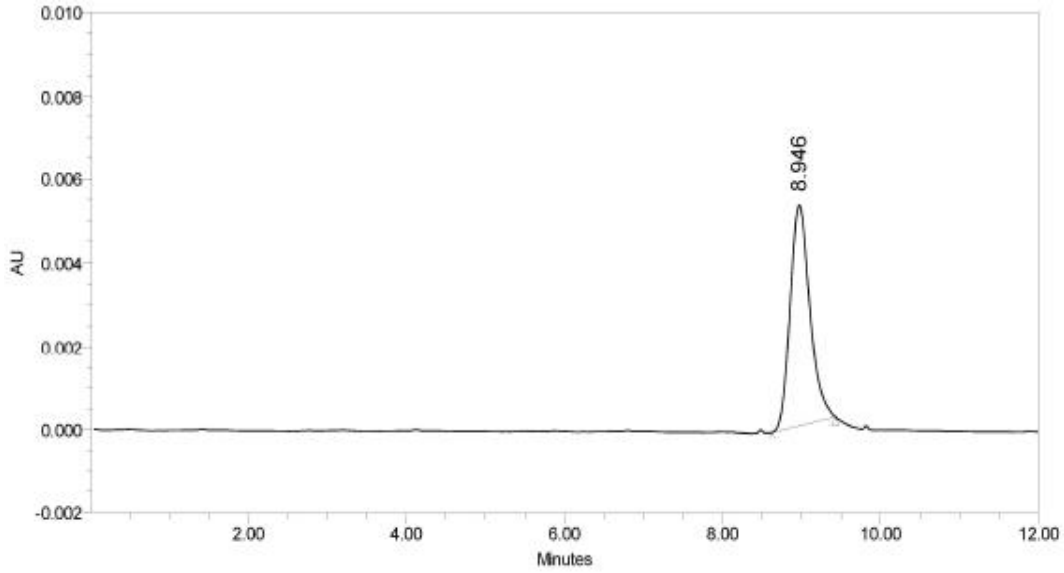
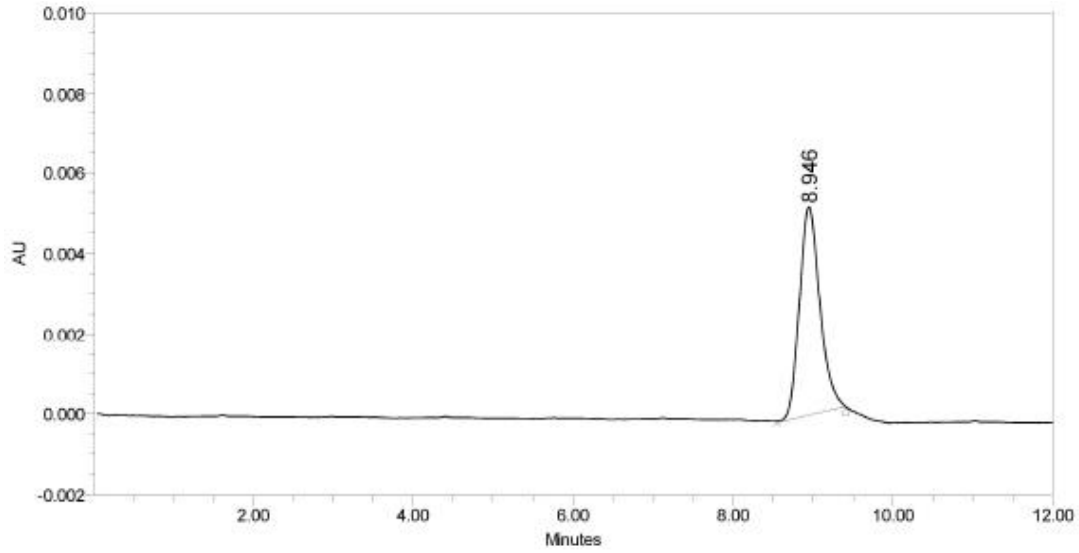


Figure 36: Peak obtained after 12 hours dissolution



The formulated floating sustained released matrix tablets were then subjected to invitro dissolution test for evaluating drug release from the formulation. The Invitro dissolution test was carried out in 900 ml of 0.1N Hcl in USP-II paddle type apparatus at 100 rpm and 37±0.5^{o}C. The results of dissolution study was depends on polymer concentration. Formulation containing HPMC K100M had given drug release 99.85% in 12 hrs. Then the formulations containing HPMC K100M were given better release profiles when compared with formulations containing Sodium CMC, PEO.

KINETIC STUDIES OF GABAPENTIN FLOATING TABLETS:

Table 32: Chart for kinetic study

Time (hours)	**Log Time**	**√Time**	**cumulative % drug release**	**Log cumulative % drug release**	**cumulative % drug remained**	**Log cumulative % drug remained**
0	0	0	0	0	100	2.000
1	0	1.000	21.32	1.328	78.68	1.895
2	0.301	1.414	32.17	1.507	67.83	1.831
4	0.602	2.000	59.09	1.771	40.91	1.611
6	0.778	2.449	66.70	1.824	33.30	1.522
8	0.903	2.828	85.68	1.932	14.32	1.155
10	1.000	3.162	94.58	1.975	5.42	0.733
12	1.079	3.464	99.96	1.999	0.150	-0.823

Figure 29: Zero order plot for F6

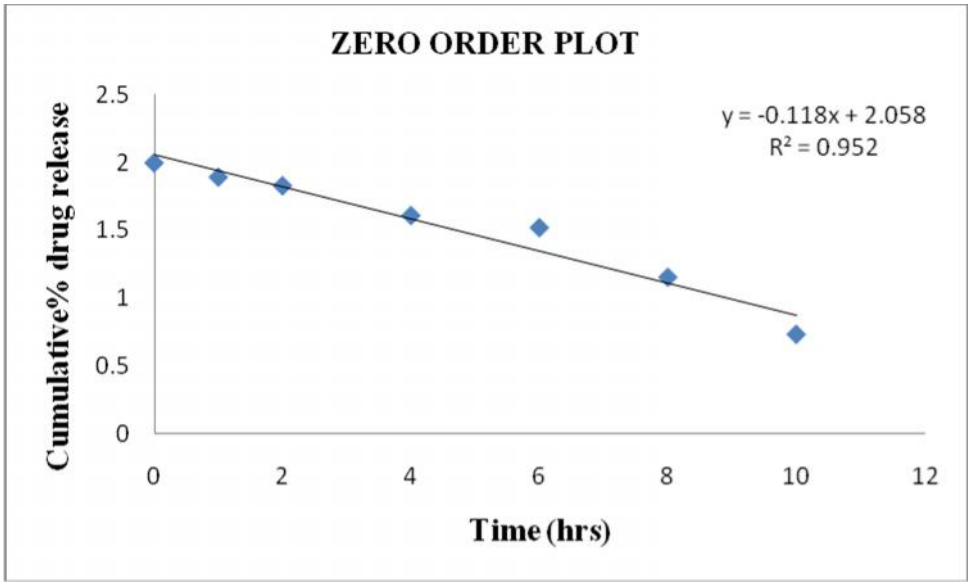


Figure30: First order plot for F6

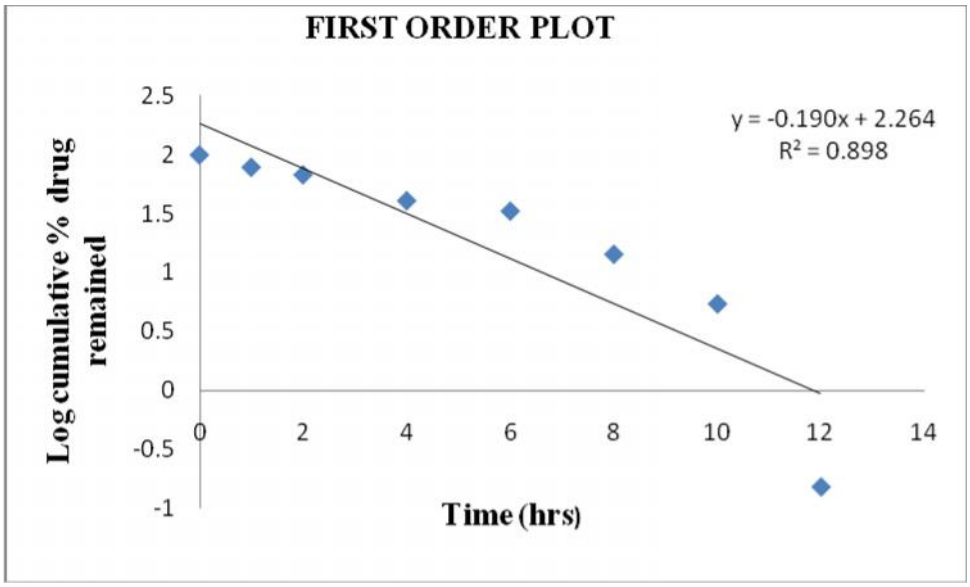


Figure 31: Higuchi plot for F6

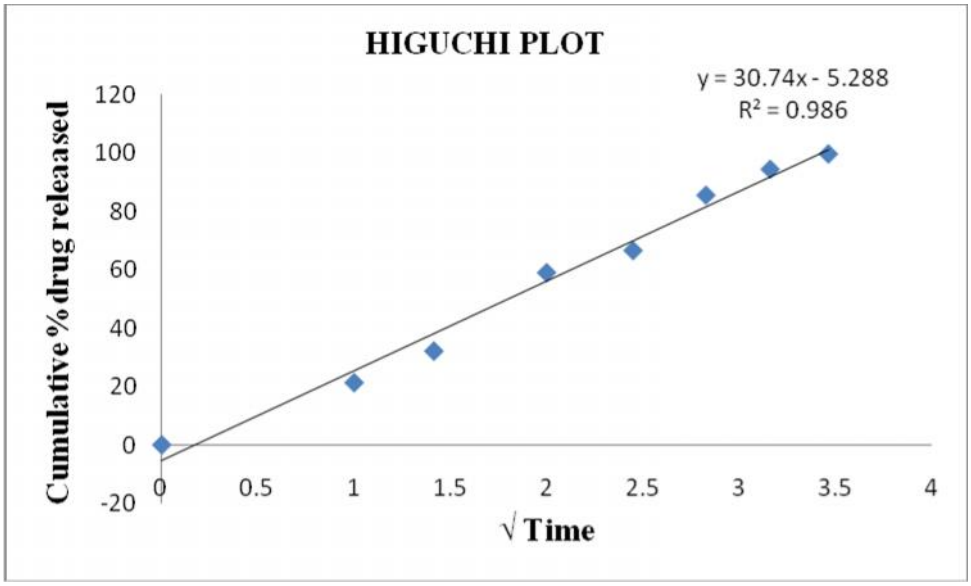
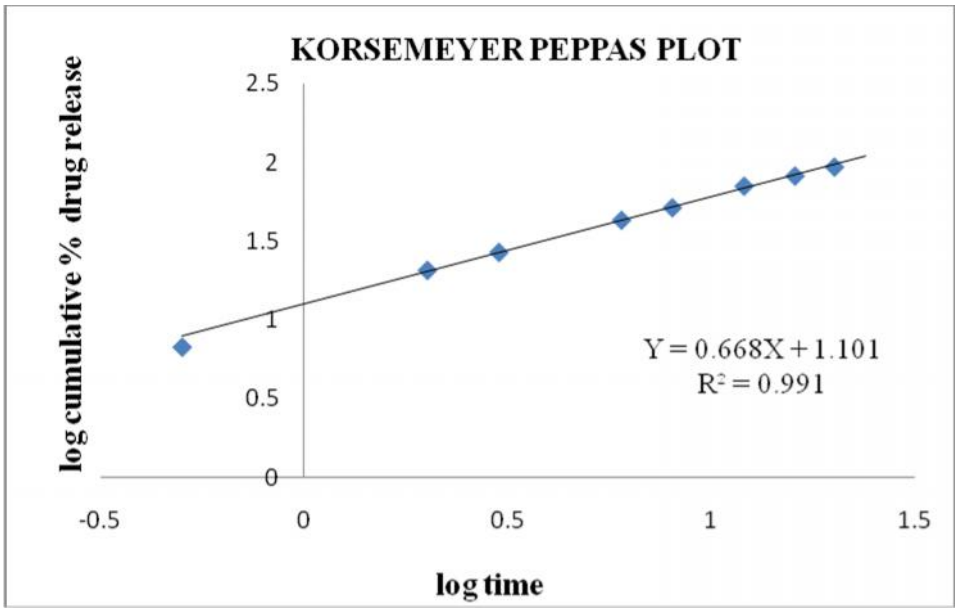


Figure 32: Korsemeyer Peppas plot for F6



KINETICS OF DRUG RELEASE

Table 33: Kinetic studies of F6

Formulation	Regression coefficient of Zero order	Regression coefficient of First order	Order of release
F6	0.952	0.898	Zero order release

Table34 :Kinetic studies of F6

Formulation	Higuchi Model		Korsemeyer Peppas Model	
	Slope	**R^2**	**Slope (n)**	**R^2**
F6	30.74	0.986	0.668	0.993

In order to determine the mechanism of drug release form the formulations, the *invitro* dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyer-peppa's plot was drawn and interpretation of release exponent value (n) was calculated . The results of R^2 for zero and first order were obtained as 0.952 and 0.798. Based on that we will confirm the optimized formulation followed Zero order release.

The drug release was diffusion controlled as the plot of optimized formulation F6 was found 0.986 as regression co-efficient in higuchi plot. From Korsemeyer peppa's plot the release exponent value n was found as 0.668 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion.

STABILITY STUDIES:

The optimized sustained release formulation was subjected to stability studies at $40^oC \pm 2^oC$ / 75% RH ± 5% for 3 months.

The product was evaluated for following parameters:

- Weight variation
- Hardness
- Friability
- Drug content
- Dissolution analysis

Storage condition at 40°C±2°C/75%RH±5%:

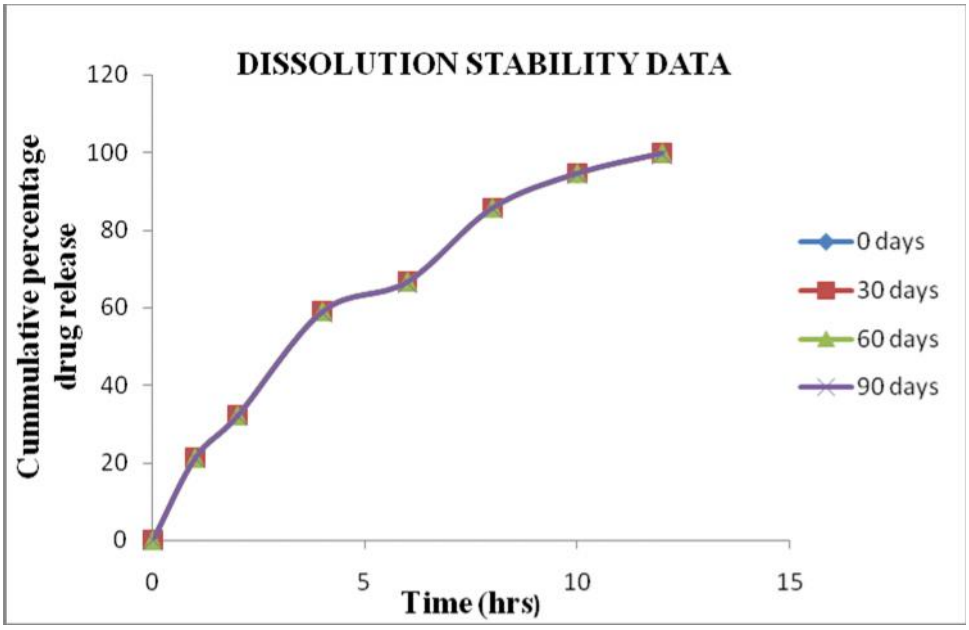
Table35: Stability data

TEST	30 days	60 days	90 days
Weight variation	949±0.55	949±0.84	948±0.69
Hardness	6.8	6.8	6.7
Friability	0.64	0.64	0.63
Drug content	99.68±0.05	99.24±0.06	99.24±0.01

Table 36: Dissolution data of percent cumulative drug release for formulation F6

Time (hrs)	0 days	30 days	60 days	90 days
0	0	0	0	0
1	21.32	21.29	21.21	21.18
2	32.17	32.15	32.10	32.02
4	59.09	59.00	58.92	58.85
6	66.70	66.64	66.58	66.50
8	85.68	85.62	85.59	85.53
10	94.58	94.55	94.50	94.48
12	99.85	99.80	99.72	99.67

Figure 33: Dissolution stability data for sample F6



The stability studies for optimized formulation F6 was carried out based accelerated stability conditions and study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that reveals that the optimized formulation was stable under accelerated condition.

Chapter VIII

Summary and Conclusion

SUMMARY AND CONCLUSION

The main objective of the present study was to develop floating sustained release formulation containing 600 mg of gabapenin for once daily therapy by using polymers like HPMC K100M, Sodium CMC, PEO. Gastroretentive Drug Delivery System improves the bioavailability and therapeutic efficiency of drug.

In the preformulation FTIR study was carried out for pure drug (Gabapentin), gabapentin and excipients. It has not shown any interaction .

The formulations were prepared by direct compression method . The angle of repose values of all the formulations ranged from 25.61±0.03 to 28.05±0.02. Bulk and tapped densities are used for the measurement of compressibility index.The bulk and tapped density values of all the formulations were ranged from 0.271±0.01 to 0.339±0.06 and 0.317±0.06 to 0.366±0.02 respectively. The carr's index and hausner's ratio values for all formulations were ranged from 12.29±0.05 to 16.35±0.03 and 1.03 ±0.05 to 1.25±0.03 respectively. Thus all formulations exhibited good flow characteristics.

The prepared floating sustained release tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The thickness of tablets in all formulations were ranged from 5.2±0.06mm to 5.3±0.05mm. The weight variation of tablets in all formulations were ranged from 948±0.15% to 952.61±0.31%.The hardness of all the formulations F1-F9 was found to be 6.4±0.2(kg/cm^2) to 7.4±0.5(kg/cm^2). The friability of all the F1-F9 formulations was found to be 0.63% to 0.76% respectively. Drug content of all the formulations were ranged from 99.11±0.14% to 99.61±0.03%. The buoyancy lag time of all the formulations were ranged from 50 Sec to 70 Sec.

Compared to all formulations F6 showed the best buoyancy lag time, the buoyancy lag time for F6 was foud to be 50Sec.Total floating time of all formulations was found to be >12 hours. The formulation containing HPMC K 100M shows the

higher swelling compared to that of the formulations containing PEO, Sodium CMC.

The prepared tablets were then subjected to dissolution test for evaluating the invitro drug release.The dissolution studies were carried out in 0.1N Hcl in USP II appatarus at 37±0.5^{o}C. The results of the dissolution studies indicated that the polymer concentration is having a substantial effect on the drug release from the tablets. Formulation F6 gave better sustained drug release and floating properties in comparision to the other formulations. This formulation took 50Sec to become buoyant.

The kinetic study was carried out for F6 formulation which showed that the drug release follows zero order kinetics.

The stability studies were carried out for F6 formulation at 40^{o}C ± 2^{o}C / 75% RH ± 5% for 3months. Data revelead that there was no considerable difference.

From the above study, it can be concluded that F6 is the optimized formulation which has shown better buoyancy time 50 Sec and drug release 99.85% . However, further in vivo studies can be carried out to support the results.

Chapter IX

Bibilography

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